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CLINICAL OBSERVATIONS UPON ATRIO-VENTRICULAR RHYTHM

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With Plates 1–4.

THE fact is well established that the mammalian heart-beat may, under certain experimental conditions, be initiated at a site intermediate in position between auricle and ventricle which is usually regarded as lying in some part of the atrio-ventricular node of Tawara.

A similar phenomenon has been observed in the human heart under various clinical conditions. In many of the clinical cases the presence of the abnormal rhythm has been accompanied by acceleration of the heart's rate, as in cases described by Hoffmann (8), Cowan (3), and others. On the other hand, some cases are on record in which the atrio-ventricular rhythm has occurred with an unchanged or with a decreased heart rate. Such cases have been described by Belski (1), Rihl (19), Kuré (11), Lewis (13), and Hume (9). In those cases in which, with the onset of the atrio-ventricular rhythm, there has been an increase in rate, it is commonly assumed that the rhythmicity of the atrio-ventricular node has become so increased that it usurps the functions of the normal pace-maker, the sino-auricular node. In several cases in which this change of rhythm with acceleration was observed by Cowan, it was found, post mortem, that the atrio-ventricular node showed inflammatory changes which had probably rendered it unduly excitable. In this connexion it may be noted that Lohmann (16) and also Kraus and Nicolai (10) obtained atrio-ventricular rhythm experimentally in animals by electrical stimulation of the region of Tawara's node. This increase of rhythmicity in the junctional tissues will not, however, suffice to explain the production of an atrio-ventricular rhythm associated with a rate of beat slower than that of the normal sino-auricular rhythm of the same case. An obvious explanation is that in these cases the rhythmicity of the normal pace-maker has become so depressed that the rhythm of the atrio-ventricular node can assert itself and initiate the heart-beat. To support this hypothesis there is a large amount of experimental work. Lohmann (17) injured the sinus node with formalin and got an atrio-ventricular rhythm, while scorching of the node

[Q. J. M., Oct., 1915.]   B

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by Hering (5), cooling of it by Lewis (14) and by Ganter and Zahn (4), and its excision by Cohn, Kessel, and Mason (2), led to the same result. These methods which depress, injure, or remove the sino-auricular node are not, however, the only means by which the atrio-ventricular rhythm can be obtained. It has been shown that it may arise from the action of the nerves controlling the heart's contraction. Lohmann (16) observed spontaneous beats arising during vagal inhibition of the rabbit's heart, which had the reduced $a.-v.$ interval characteristic of atrio-ventricular rhythm. Rihl (20) and Hering (7) obtained similar shortening of the $a.-v.$ interval by sympathetic stimulation. These results have been confirmed by more recent work, for Rothberger and Winterberg (21) produced atrio-ventricular rhythm in 30 per cent. of their experiments by stimulation of the left sympathetic, while Meek and Eyster (18) produced it in two out of twenty-seven experiments by stimulation of the right vagus. Kuré (12) stimulated the cardiac nerves by asphyxia and obtained the rhythm in this way. Belski's (1) work affords a clinical parallel as regards vagus stimulation, for, in cases which had a tendency to assume the rhythm spontaneously, he was able to induce its appearance by pressure over the vagus in the neck.

Atrio-ventricular rhythm produced in these various ways has certain distinguishing features in graphic records. The $a.-v.$ interval becomes reduced, and may disappear entirely or even become negative, the ventricle slightly preceding the auricle in contraction. In electro-cardiograms the form of the auricular deflexion P is altered, becoming inverted, while in polygraphic records the auricular wave a in the venous pulse disappears from its normal presystolic position and becomes more or less completely fused with the carotid wave. When these changes are found in graphic records it is commonly agreed that the atrio-ventricular node initiates contraction. This view rests upon experimental observations. Hering (6) showed that the delay in transmission of stimuli from auricle to ventricle occurs in this node, so that when the $a.-v.$ internal is reduced the stimulus cannot be regarded as originating in any part of the auricular musculature outside the node. That the stimulus is not ventricular in origin is proved by the fact that in electro-cardiograms of the atrio-ventricular rhythm the ventricular complexes have the form associated with supra-ventricular stimulus formation. Thus the rhythm must have its origin in Tawara's node or in the bundle immediately beyond it.

An important confirmatory observation was made by Zahn (24), who found that during an atrio-ventricular rhythm produced by cooling the sinus node, the rate of the heart-beat was affected by heat and cold applied to Tawara's node, but not by their application to other parts. The most convincing proof, however, of the origin of this rhythm in the atrio-ventricular node has been furnished by the work of Meek and Eyster (18), who, using the method of Lewis (15) and Wybauw (23), found that the site of primary negativity during the rhythm lies in the node. The inversion of the auricular deflexion P in electro-cardiograms furnishes another ground for the belief that the atrio-ventricular node is the site of impulse formation, as Lewis found that such inversion occurs when contraction

is induced by stimulation of the lower zone of auricular tissue, i.e. the region of the node.

In a case recently observed by the present writer it was found that a rhythmical alteration was occurring in the mode of contraction of the heart as revealed in graphic records, for an atrio-ventricular rhythm appeared at intervals. The rhythmic change was not synchronous with the respiration. Polygraphic and electro-cardiographic records were obtained, and as it seemed probable from the nature of the case that altered innervation played at least a part in determining the change of rhythm, observations were made of the effects produced on the mode of contraction by stimulation or depression of the functions of the controlling nerves. The clinical features of the case are first briefly described, an account of the graphic records obtained is next given, and finally various features of the case are discussed with their relation to those described in similar cases in the literature.

Clinical Notes.

F. R., aged 22, a miner, was admitted on March 24, 1915, to the wards under the charge of Professor Sir T. R. Fraser in the Royal Infirmary, Edinburgh.

He complained of shortness of breath and unpleasantly forcible action of the heart, both of which had troubled him for a year and occurred only on exertion. No history of any rheumatic symptoms, sore throat, or venereal infection could be obtained, the patient stating that the only illness he could remember was a slight appendicitis two years before. The patient was a teetotaller and smoked 10–12 cigarettes a day. His work involved the moving of heavy hutches of coal. He was an intelligent lad, rather thin, but presenting no other appearance of ill health. The pulse-rate was about 70 per minute and the rhythm was apparently regular. The blood-pressure in the brachial artery was 120 mm. Hg. systolic, and 85 mm. Hg. diastolic. The apex-beat of the heart was in the fifth left intercostal space and was diffuse. A well-marked systolic thrill was palpable over it. A long rough systolic murmur was heard on auscultation over the apex. Systolic murmurs were audible also over the base of the heart and at the foot of the sternum. The character of the first sound, as heard at the apex, varied, becoming at times very loud and sharp. During this accentuation of the sound the systolic murmur was longer and louder. The cardiac dullness extended 1¼ inches to the right of the middle line and 4¼ inches to the left at the level of the fourth costal cartilages. Venous pulsation was visible in the neck. The urine contained no abnormal constituent and the other systems appeared to be healthy.

No drug of the digitalis group was given before or during the observations.

Graphic Records.

The first electro-cardiogram (Fig. 1) was taken, by Derivation II, on a slowly moving plate in order to include several of the short periods of each rhythm and to show their alternate appearance. A respiratory record is shown with it. The changes in form are quite clearly visible, but the exact mode of transition from one rhythm to the other is more readily studied in records from faster plates. Such a series is shown in Figs. 3 *a*, 3 *b*, and 3 *c*, taken by Derivations I, II, and III

respectively.   In Fig. 3 *a* (Derivation I) the first three beats show a normal sino-
auricular rhythm with a rather long *P–R* interval, 0·18–0·19 sec.   The next
three beats show a steady decrease in the length of the *P–R* interval (0·14, 0·12,
and almost 0), and in all the succeeding beats, except the last, *P* appears
between *R* and *T*, attaining gradually a maximal displacement beyond *R* and
creeping back towards it again, to become merged in it in the last beat, which
resembles the sixth.   It is noteworthy that the *P* deflexion retains its upright
form even when it is displaced beyond *R*.   In the records by the other
derivations *P* becomes gradually inverted as the displacement occurs.   Changes
occur also in the ventricular complex, the *S* and *T* deflexions becoming more
pronounced when the abnormal rhythm is assumed.   Even in the third beat,
before the *P–R* interval is appreciably shortened, this change is visible.   As
regards the length of the heart cycles it is found that, measuring from the
beginning of each *R* to the next, they are all of practically equal length.[1]

Fig. 3 *b* (Derivation II) shows a similar gradual shortening of the *P–R*
interval from 0·19 secs. in the first five beats to 0·17, 0·14, 0·08, 0·01, 0 sec. in the
succeeding ones.   The *P* deflexion has not changed its position far enough beyond
R in this record to show its inversion clearly, but this is seen in other records
by the same derivation (Fig. 6).

Fig. 2.   Polygraphic record of alternating rhythms.

A marked change in the form of the ventricular complex is seen from the
sixth beat onwards.   The *R* and *T* deflexions are increased and decreased in
height respectively.   The smaller *R* of the eighth beat is due to interference by
the *P* deflexion.   The heart cycles, measured as before, are of equal length.

Fig. 3 *c* (Derivation III) shows in the first three beats a decreasing *P–R*
interval, 0·17, 0·12, 0·3 sec., after which *P* appears inverted between *R* and *T*
for four beats.   It then reappears in the upright position before *R* and the *P–R*
interval increases to 0·19 sec. in the last four beats.   Here again the change in
the ventricular figure is striking.   *R* is greatly increased in height during the
beats with reduced *P–R* interval, while *T* is diminished in size.   The first eight
cycles from *R* to *R* are of equal length.   The remaining cycles are shorter.

Fig. 2 shows the appearance of the alternating rhythm in a polygraphic
record.   The normal *a–c* succession of the venous tracing is replaced at intervals
by a large wave, synchronous with ventricular systole and produced by the

[1] Owing to unequal rate of movement of the plate the cycles appear unequal.   Each
must be measured from that part of the time record directly beneath it.

simultaneous contraction of auricle and ventricle. This interpretation is borne out by Fig. 4, in which the electro-cardiogram (Derivation I) and the venous tracing appear together.

The polygraphic record shows a rather prolonged a–c interval of 0·25 sec., corresponding with the increased P–R interval in the electro-cardiograms. The rate of the heart-beat decreases in Fig. 2 during the atrio-ventricular rhythm.

While the records from the patient usually presented the alternating rhythm, there seemed to be at times a tendency for the atrio-ventricular rhythm to gain the upper hand and appear continuously for longer periods. The differing forms of the electro-cardiographic complexes during the two rhythms were easily distinguished by an observer watching the magnified image of the moving string, and it was noted that while the atrio-ventricular rhythm might persist at times for about ten minutes, the normal rhythm was never continued for more than about twelve consecutive beats except under the influence of nerve stimulation or depression.

Fig. 5 (Derivation II) shows a period of persistent atrio-ventricular rhythm. A peculiar feature in it, which was observed in other records also, is that while P never attains its normal place there is a variation in its position. In some beats it has a more obvious inversion and a greater depth than in others, dependent on the degree of its displacement beyond R. The remaining electro-cardiograms show the effect on the heart's contraction of stimulation or depression of its controlling nerves. They are all taken by Derivation II.

Vagus Stimulation.

This was carried out by digital compression over the carotid sheath in the neck. Repeated observations were made of the effect of digital compression of the right and of the left vagus during the usual alternating rhythm, during the more prolonged periods of atrio-ventricular rhythm, and during sino-auricular rhythm produced by exercise as described below.

In no case was pressure upon either vagus found to produce any alteration in the rhythm prevailing at the time of stimulation. There was not even any distinct slowing of the rate obtained, nor any interference with conduction. Figs. 6, 7, and 8 show vagus pressure applied during the alternating, atrio-ventricular, and sino-auricular rhythms respectively.

The change in form and position of the P deflexion in Fig. 7 cannot fairly be ascribed to the stimulation of the vagus, for it was observed in other records of the atrio-ventricular rhythm apart altogether from vagus stimulation (Fig. 5).

Vagus Paralysis.

The cardiac fibres of the vagus were paralysed by a subcutaneous injection of $\frac{1}{30}$ grain of atropin sulphate. Before the injection the patient's heart showed a preponderating atrio-ventricular rhythm with a few normal beats at long intervals. Fig. 9 was obtained just before the injection. The rate is 63 per

minute. No change was noticed on watching the movements of the string during the first quarter of an hour. An electro-cardiogram taken fifteen minutes after the injection showed no change in rhythm or in rate.

Soon after this, runs of normal beats were observed, and twenty minutes after the injection a record showed a completely normal rhythm at 68 per minute. This rhythm persisted and the rate of heart increased. Fig. 10, taken thirty minutes after injection, has a rate of 78 per minute and a P–R interval of 0·17 sec.

The normal rhythm was observed to persist for another quarter of an hour, when observations were discontinued. An electro-cardiogram taken $3\frac{1}{2}$ hours after the injection showed a return to the preponderating atrio-ventricular rhythm with occasional short groups of normal beats.

Summary of above:

12.56 p.m.	Preponderating atrio-ventricular rhythm. Rate, 63 per minute.
12.58 p.m.	Atropin sulphate (gr. $\frac{1}{30}$) injected.
1.13 p.m.	No change.
1.18 p.m.	Sino-auricular rhythm, 68 per minute.
1.28 p.m.	Sino-auricular rhythm, 78 per minute.
4.25 p.m.	Preponderating atrio-ventricular rhythm. Rate, 66 per minute.

Sympathetic Stimulation.

It was noticed on several occasions that when the patient had walked quickly from the ward to the laboratory the heart beat with the sino-auricular rhythm for some minutes after observations were begun. The effect of gentle muscular exercise was therefore observed during the alternating rhythm. This was done by making the patient flex and extend the left arm at the elbow. It was constantly found that, as soon as the movements began, the sino-auricular rhythm was established, and persisted as long as the movements were continued and for a short time afterwards, when the original alternating rhythm reappeared. This procedure was repeated many times and never failed to evoke the sino-auricular rhythm. Fig. 11 shows this effect. The period of exercise is marked by electric signal. There could be no doubt as to the influence of the movements in producing this change, for, apart from muscular exertion or the use of atropin, the patient never showed more than about a dozen continuous sino-auricular beats and very rarely so many. The P–R interval of the sino-auricular rhythm induced by exercise was 0·19 sec., in records taken on faster plates where measurement was possible. The rate of the beat was always increased by the exercise. The current physiological teaching as to the mechanism by which muscular exercise accelerates the heart-beat is that the principal factor is sympathetic stimulation, while stimulation of the heart muscle by metabolic products of exercise plays a subsidiary part. It may, I think, be safely assumed that the almost instantaneous effect recorded above was produced by sympathetic stimulation.

General Discussion.

The nature of the change in the heart's contraction in this case seems to be clearly established, for the electro-cardiograms show changes exactly similar to those seen in records of atrio-ventricular rhythm produced experimentally. There are some points of interest in the case considered from a clinical standpoint. The most interesting feature revealed by the ordinary clinical methods of examination is the rhythmic change in the character of the first sound and its accompanying murmur. Belski (1) records a similar change in the sound in cases of rheumatic fever which presented periods of atrio-ventricular rhythm, but in his cases the sound was accentuated during the atrio-ventricular rhythm, while in the present case it was relatively diminished. In attempting to find an explanation for this change in the sound, the state of the mitral valve in this patient must be remembered. It was incompetent, and this was almost certainly due to structural changes in the valve flaps or chordae tendineae resulting from some former endocarditis. The part which the closure of the mitral valve normally plays in the production of the first sound was, therefore, probably lessened, and the sound, so far as it is valvular, may be attributed mainly to the closure of the tricuspid valve.

During the normal sequence of contraction in auricle and ventricle there is no obstruction to the forcible closure of the tricuspid valve by the contracting right ventricle, but during the atrio-ventricular rhythm we have the chambers on each side of the valve contracting simultaneously, and while the ventricular pressure will speedily overcome the auricular, the latter may be sufficient to render the closure and tension of the valve cusps less abrupt and forcible and so less audible. The decreased intensity of the mitral murmur may be explained in a similar way, for the regurgitant stream of blood will meet the opposing current produced by auricular systole, and may thus be checked and diminished in speed or in amount.

The other possible cause of the variation in the sound is an alteration in the force of the ventricular muscle's contraction. No evidence for this view was found in the polygraphic tracings. There was no constant difference in the size of the radial beats during the two rhythms.

The other point of clinical interest is the fact that no disagreeable symptoms were produced even during the longer periods of the atrio-ventricular rhythm and the circulation seemed well maintained.

It must be remembered that in all probability the normal rhythm was established during any considerable exertion undertaken by the patient. This deduction seems permissible from the observed effects of muscular exercise and may explain the absence of any symptoms under these circumstances.

Turning to the points revealed in the graphic records, it is seen that during the periods of sino-auricular rhythm there was always some impairment of conduction shown by the prolonged a–c and P–R intervals. The reduction of the interval during vagus paralysis by atropin suggests that the defect in

conduction may have been due to increased tone of the vagus. The gradual shortening and lengthening of the P–R interval during transition from one rhythm to another may next be considered. One view advanced by several observers ascribes this to a gradual shifting of the site of primary stimulus formation backward and forward between the sino-auricular and atrio-ventricular nodes. It is clearly seen, however, from the electro-cardiograms that the interval may become greatly shortened without any alteration in that form of the P deflexion which the work of Lewis has associated with stimulus formation in the normal site. Meek and Eyster (18) found a similar condition during the change from an atrio-ventricular rhythm to a normal one. They considered the possibility of increased facility in conduction through the atrio-ventricular node as an explanation of the reduced interval. It seems more likely in the present case that the association of a normal P deflexion with a reduced P–R interval indicates the temporary response of auricle and ventricle to separate sites of stimulus formation, as suggested by Rothberger and Winterberg (21), Kuré (12), and others.

The recorded cases which the present one most closely resembles are those of Belski (1) and of Rihl (19). In some of Belski's cases the change of rhythm occurred frequently, and the atrio-ventricular rhythm could be abolished by atropin and produced by vagus pressure, suggesting increase in vagus tone as the cause of the abnormal rhythm. One of Rihl's cases in which the rhythms alternated at the same rate is ascribed by him to increased vagus tone. A similar explanation for the present case may therefore be considered. Evidence for this view is found in the effect which atropin had in abolishing the atrio-ventricular rhythm by vagus paralysis. The effect of vagus stimulation by pressure did not, on the other hand, lend any support to this view, for it showed no tendency to produce or to maintain the abnormal rhythm. Pressure, however, seems in many persons to be ineffective as a means of vagus stimulation. As the sympathetic is opposed to the vagus in its action on the heart, it is of interest to find the atrio-ventricular rhythm abolished during sympathetic stimulation. The changing position of the P deflexion in different beats of the atrio-ventricular rhythm is noticeable in some of the electro-cardiograms (Figs. 5 and 7). This change has been recorded by several observers as occurring when the vagus is stimulated during experimentally produced atrio-ventricular rhythm. Kuré (12) and Meek and Eyster (18) explain it as produced by the shifting of the site of stimulus formation from one part of the atrio-ventricular node to another, while Lewis (14) ascribes it to the production of reversed block between the atrio-ventricular node and the auricles. In the present case the passage of P to its farthest point beyond R may be supposed to occur when the wave of increased vagus tone reaches its maximum. The changes in the form of the ventricular complex which occur as the atrio-ventricular rhythm is established may also be adduced in support of its vagal origin, for the increase in height of R and the flattening of T (Fig. 2 c) closely correspond to the changes obtained in electro-cardiograms during vagus stimulation by Rothberger and Winterberg (22).

On the whole it seems probable that recurrent increase of vagus tone may have produced the phases of atrio-ventricular rhythm in this case, but the nature of the mechanism of its action is not obvious. The assumption of an atrio-ventricular rhythm with a rate the same as, or slightly less than, that of the sino-auricular rhythm seems, in this case, to necessitate two changes to explain it, a decreased sinus rhythmicity and an increased rhythmicity of the atrio-ventricular region. The first is not the only factor, for the records indicate that the ventricle begins its response to a new site of stimulus formation before there is any alteration of sinus rhythmicity evident. It may be supposed either that the vagus is capable of depressing the rhythmicity of the sino-auricular node while increasing that of the atrio-ventricular, or that some organic change exists in the heart muscle, which has increased the rhythmicity of the latter node to a level almost equal to that of the former, so that the atrio-ventricular node can at times initiate independent ventricular contraction and can control auricular contraction also when the activity of the sino-auricular node becomes depressed by vagus action.

In conclusion, I desire to acknowledge the kindness of Professor Sir T. R. Fraser in permitting me to make observations upon the case.

Summary.

A case is recorded which displayed a rhythmic change in the mode of the heart's contraction. Graphic records showed that the beat was initiated by the sino-auricular and atrio-ventricular nodes alternately.

A corresponding rhythmic change in the first sound and in an accompanying mitral murmur was observed on auscultation.

The rate of the beat during the atrio-ventricular rhythm was either equal to, or slightly less than, that of the periods of normal rhythm.

Observations were made on the effect produced by stimulation and depression of the controlling nerves upon the heart's mode of contraction.

Recurrent increase of vagal tone is suggested as a possible explanation of the alternating rhythm.

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DESCRIPTION OF FIGURES.

In each record the tension of the string was adjusted so that, with a magnification of 600 diameters, a difference of potential of 1 millivolt introduced into the circuit containing the galvanometer and patient gave a deflexion of 1 cm. The tuning-fork record in the figures is 28·57 per second.

Electro-cardiograms are taken by Derivation II unless otherwise stated.

PLATE 1, FIG. 1. Alternating rhythms. Respiratory record above.

FIG. 3 *a* (Deriv. I) ; FIG. 3 *b* (Deriv. II); PLATE 2, FIG. 3 *c* (Deriv. III). Transition from one rhythm to the other.

PLATE 2, FIG. 4. Simultaneous record of electro-cardiogram (Deriv. I) and jugular tracing. Alternating rhythms.

FIG. 5. Persistent atrio-ventricular rhythm. Variation in position of *P*.

PLATE 3, FIG. 6. Pressure upon right vagus during alternation of rhythm.

FIG. 7. Pressure upon right vagus during atrio-ventricular rhythm.

FIG. 8. Pressure upon right vagus during sino-auricular rhythm.

PLATE 4, FIG. 9. Atrio-ventricular rhythm, 63 per minute, just before injection of atropin.

FIG. 10. Sino-auricular rhythm, 78 per minute, 30 minutes after injection of atropin.

FIG. 11. Effect of muscular exercise upon alternation of the rhythms. Sino-auricular rhythm established.
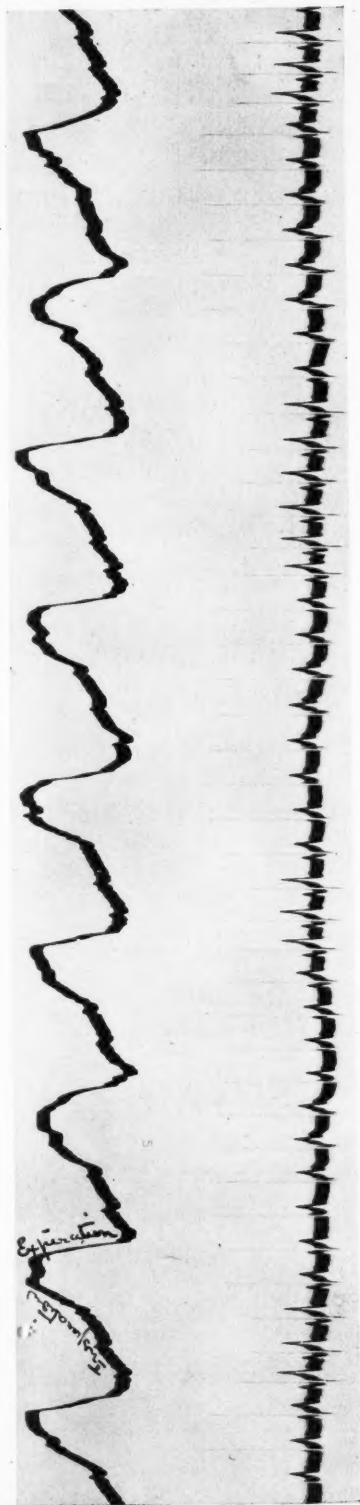
Fig. 1

Fig. 3a
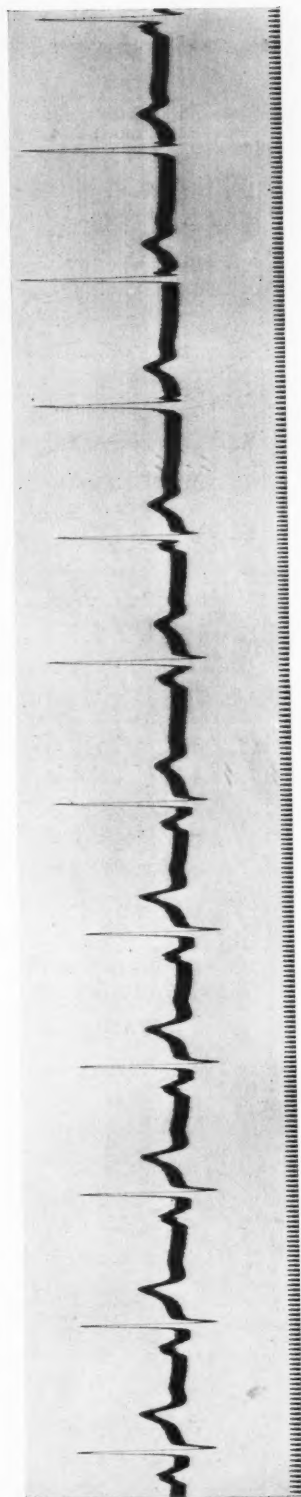
Fig. 3b

FIG. 3c
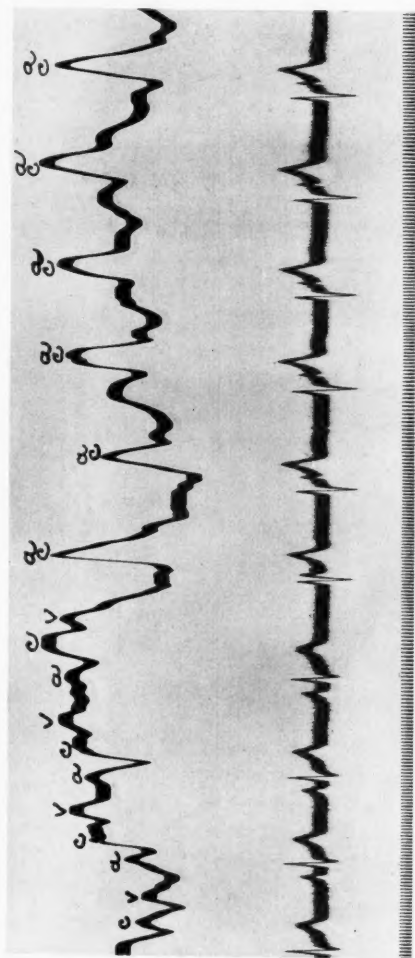
FIG. 4
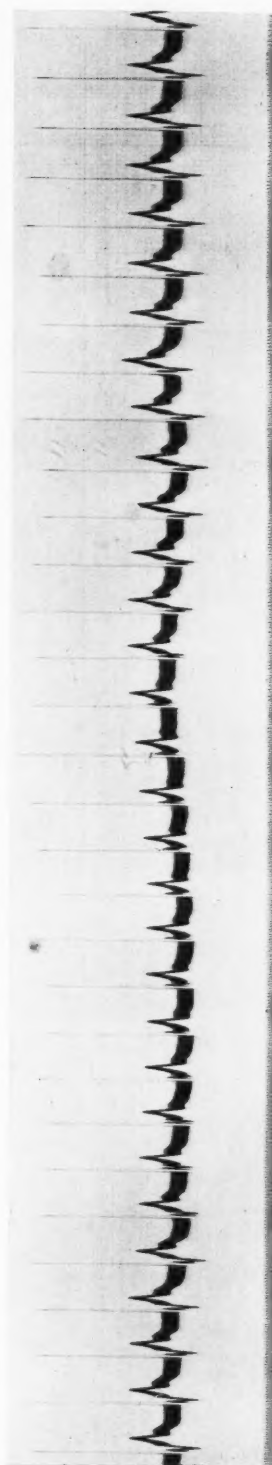
FIG. 5
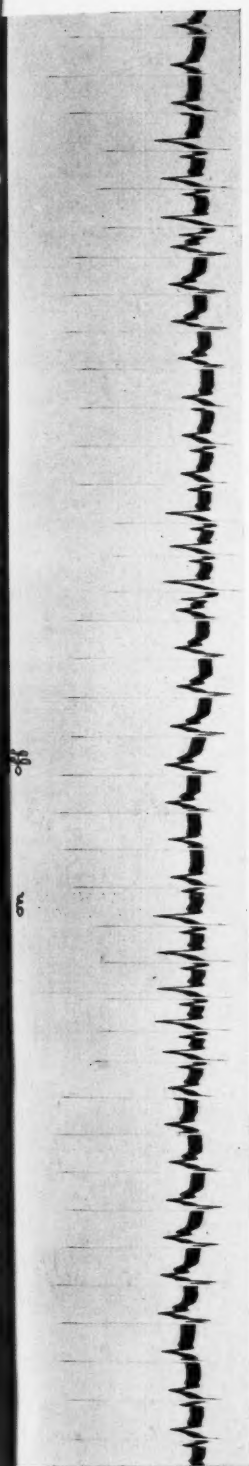
Fig. 6
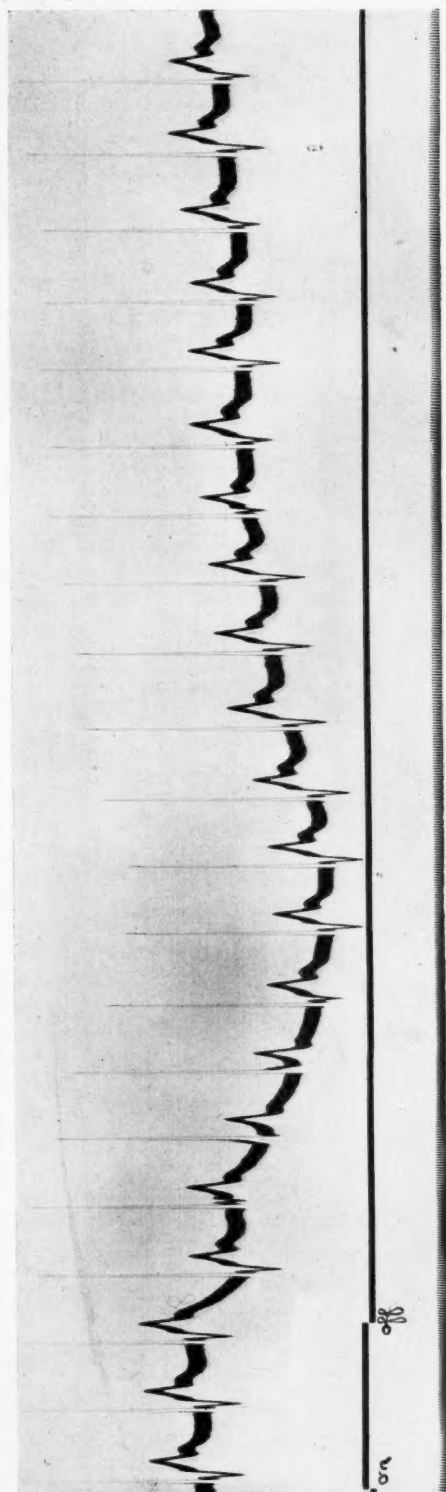
Fig. 7

Fig. 8

Fig. 9

Fig. 10
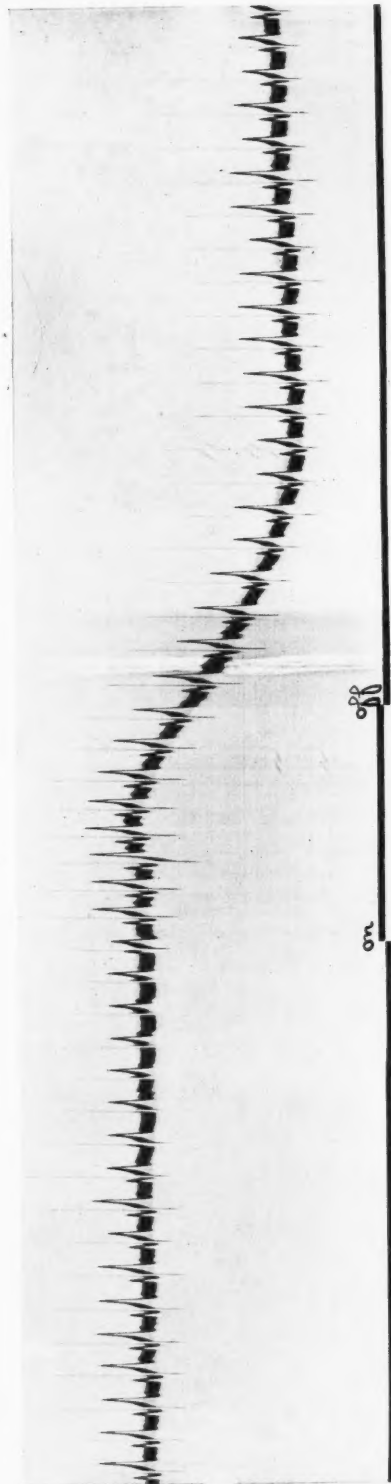
Fig. 11

A CASE OF PANCREATIC INSUFFICIENCY

BY E. I. SPRIGGS AND A. J. LEIGH

(From the Chemical Laboratory, Duff House, Banff)

CONTENTS.

Introduction.

OUR knowledge of the disturbances of nutrition which accompany chronic disorders of the pancreas has grown much in recent years, as a result both of experimental work in animals and of pathological observations in man. There are, however, but few published cases in which a consecutive series of analytical data from both urine and faeces is available.

On admission, therefore, to Duff House of a patient who had been the subject for some years of a deficient assimilation which appears to be due to pancreatic disease, we took the opportunity of recording the composition of the food and excreta.

Clinical Account.

The patient, a man of sixty, complained of wasting, muscular weakness, thirst, glycosuria, and of very bulky motions, after passing which he was obliged to lie down for some time.

His mother, who died at the age of 69, was the subject of glycosuria.

Twenty-five years ago the patient had several attacks of violent pain in the epigastrium, attributed at that time to indigestion. Some years later he had four or five attacks of a different nature, at intervals of from one and a half to two years, which proved to be due to appendicitis. The diseased appendix was removed thirteen years ago, in 1901. He remained well until four years ago

(1910), when he suffered from loose, bulky motions, and consulted Dr. Cammidge, who, finding, by the Werner-Schmidt method, 79 per cent. of fat in the dry matter of the faeces, and a high iodine coefficient, told him that there was a likelihood of sugar appearing in the urine later. In 1911 pustules appeared about the body and were treated with a vaccine. In this year, sugar was found, and has appeared from time to time since, but has also been absent for considerable periods even when a fair quantity of starchy food has been taken and particularly when the patient has been away for a rest and change. He has lost two stone in weight in the last four years. There has sometimes been urgency of micturition and of late thirst. The patient does not feel especially hungry, but has been noticed to eat a great quantity of food.

Large, pale-coloured and loose motions have been passed for years, usually twice a day. Defaecation is very exhausting.

The patient has taken a prominent position in commercial and political life, and his public and private engagements have involved much travelling and responsibility.

Examination on admission. (December 10, 1913.) The skin was loose, and gave the appearance of the patient having become much thinner ; it was not dry. There was no jaundice.

There were a few pustules, chiefly about the fingers.

The tongue was furred. The teeth were in good order. No abnormal signs were found in the abdomen or chest. Blood-pressure, 120 mm. Hg.

Blood examination. Haemoglobin, 85 per cent. Red blood corpuscles, 5,160,000. White blood corpuscles, 10,400. Differential count :—polymorphonuclears 60·4 per cent. ; small lymphocytes, 19·2 per cent. ; large lymphocytes, 11·2 per cent. ; transitional cells, 8·4 per cent. ; mast cells, 0·4 per cent. ; eosinophil cells, 0·4 per cent.

Urine. 2,270 c.c. in the twenty-four hours. Acid. Total nitrogen, 15·8 grm. Uric acid, 1·04 grm. Sugar, 79 grm. No aceto-acetic acid, acetone, albumin, or blood. Many oxalate crystals.

Faeces. About 1,000 grm. in the day of a semi-liquid character, becoming more solid in cooling, grayish-yellow, with a non-foetid rancid odour. Acid. Hydrobilirubin was present, but tests for bile acids and salts were negative. On microscopical examination abundant sheaves of crystalline needles and amorphous droplets were seen, also many striated muscle fibres. The Gram-positive organisms were in a minority. Starch granules were rare.

Analysis. Dry matter, 40 per cent., containing 73 per cent. of fat (290 grm. in the day) 3·73 nitrogen (15 grm. in the day); 6·2 per cent. of ash. Starch test :—the residue after the extraction of fat, when hydrolysed, gave only a trace of reduction.

Tests for Pancreatic Efficiency.

Keratin capsules. A keratin-coated capsule (Martindale) containing 0·3 grm. of Methylene blue was given on two occasions, once in the morning and once at night. In each case the colour appeared in urine passed six to nine hours later. Capsules taken by another patient with diabetes of the usual type, and by a healthy man, gave a similar result.

Sahli's capsules. One of Sahli's 'glutoid' capsules, made of gelatin hardened with formalin, and containing 0·15 grm. of iodoform, was taken by the patient, a healthy control taking another of the capsules. The saliva of both was tested at hourly intervals. The iodide reaction appeared in that of the control in eight hours, and remained for fifteen hours. No reaction was obtained from the saliva of the patient.

Thymus nuclei test. Kashiwado's modification of Schmidt's cell-nuclei test was used. The nuclei from the thymus gland are isolated and stained with iron-haemotoxylin and mixed with lycopodium. The test is reported to have

been found reliable in animals, and in a case of complete obstruction of Wirsung's duct. No blue nuclei were seen, but as the lycopodium spores were not easily identified in the fatty faeces the test cannot be regarded as of value in this case.

Trypsin in faeces. The faeces were examined for trypsin by comparing the digestive power of a watery extract with that of a similar extract from normal faeces (*a*) upon fibrin stained with congo red, and (*b*) upon casein, by Franke and Sabatowski's modification of Gross's method. (*a*) Both extracts dissolved fibrin to some extent, but the solution was more marked in the extract from the normal faeces. (*b*) No digestive power upon casein was found in the extract from the patient's stools on three occasions, whilst in controls from the stools of two normal persons casein was digested.

The value of this test is discounted in theory by the fact that it has occasionally been found that trypsin cannot be detected in the faeces of a healthy person (28).

Diastase in faeces. Great variations are found in the quantities of diastatic ferment in normal faeces, but its absence or low value is in favour of the absence of pancreatic juice. In this case a very low value was obtained (32) (41).

The diastatic value of the urine was determined by Corbett's modification of Wohlgemuth's method on five occasions, and found to be low, the index $d\,\dfrac{38°}{30'}$ varying from 2 to 5 units, the normal value being 10 to 20. The quantity of urine in these days was about 3,000 c.c., so that, taking this into consideration, the amount of diastase approximates to the normal. The amount of diastatic ferment in the urine has been found to be raised in acute disease of the pancreas, or at the onset of increased disturbance of function in chronic disease (28).

Corbett found an increase in a number of cases of carcinoma of the pancreas, and in various other pancreatic affections, such as miliary tuberculosis with fibrosis of the pancreas, pancreatitis with jaundice, and jaundice with probable pancreatitis, but we have not found a record of a case of this nature, with the typical bulky and fatty stools persisting for years, in which the diastatic value has been reported to be raised.

This case does not therefore support the statement that the test is positive in every kind of pancreatic lesion (32).

Diagnosis.

The gradual onset, without jaundice, of fatty stools of enormous bulk in which more than half the fat in the food and one-third of the nitrogen was lost, the wasting, and the glycosuria, taken with the failure to demonstrate trypsin in the faeces, lead to the conclusion that the pancreas is diseased. The duration of the symptoms and the absence of a tumour make it improbable that there is malignant growth involving that organ. A slow but extensive atrophy of the gland appears to be the most likely condition, probably secondary to calculi.

Conduct of Case.

The investigation of the case was conducted with a view to finding out what foods the patient was best able to assimilate, in order that his nutrition might be re-established so far as possible, and his medical advisers furnished with information which would guide them in directing his diet. Owing to the patient's engagements his stay at Duff House was an interrupted one.

It is obvious that in a case in which a large proportion of proteins, carbo-hydrates, and fats was lost in the faeces and urine, the problem of feeding became difficult. The chief hope of improving the nutrition lay in getting rid of glycosuria and increasing the tolerance for carbohydrates : fortunately this could easily be done.

Throughout the observations all the food given to the patient was weighed, any food that was left being also weighed, so that the amount consumed daily of each article of diet was known. This is done with most of the diets in Duff House, so that it is carried out by accustomed hands, and the figures, though not as accurate as those obtained by giving exactly the same food every day, are as nearly so as the circumstances allow. From these records the amounts of proteins, carbohydrates, and fats were calculated daily.

For one period, period P, the patient was on Schmidt's standard diet, the same diet being taken at the same time by a healthy man, whose excreta were also analysed. A third portion of the same foods was set aside for analysis, the results of which agreed closely with the calculated figures.

The figures given for the diet in each experimental period are the average figures per diem of the diet in that period.

In the series of observations which were reported at the Association of Physicians in March, 1914, viz. periods A to M, we found unexpected variations in the composition of the special diabetic breads which the patient took. These variations affected our figures to some degree, though they were not sufficient to vitiate the general conclusions. Nevertheless, in order to make sure, we repeated the observations (P to U), after this source of error had been dis-covered. All diet figures upon which this suspicion fell are omitted from the tables. A year later the patient returned to Duff House, and the opportunity was taken of making further analyses for three periods of two days each (V, W, and X).

In all, five series of observations were made, various diets, ferments, and preparations being given for periods of two or three days.

TABLE I.

Series.	Date.	Number of Days.	Diet Periods.
I.	Dec., 1913	4	
II.	Jan., 1914	15	A to F
III.	Feb., 1914	18	G to M
IV.	March and April, 1914	15	P to U
V.	April, 1915	6	V to X

Total 58 days

Analytical Methods.[1]

The urine was collected daily from 8 a.m. to 8 a.m., and the nitrogen determined in the twenty-four hours' specimen by the Kjeldahl process. Sugar, when present, was estimated gravimetrically as cupric oxide.

[1] The analyses were all made by A. J. L.

Each stool was weighed when received in the laboratory, well-mixed, and 3 per cent. of it, that is, 30 grm. per kilo, weighed and evaporated to dryness with absolute alcohol on a boiling water bath. A further portion of about 250 grm. was also dried and reserved for control analyses. The sample was placed in the steam oven for about an hour, allowed to cool in air, weighed, powdered with as little loss as possible, reweighed and heated in the oven at 100° for several hours, cooled in a desiccator, and again weighed, the heating being repeated until no further loss to one centigramme was found.

The dry samples of the three-day periods were mixed and thoroughly ground together, and again heated in the oven for a short time before the various portions were weighed out for estimation of fat and nitrogen.

From 6 to 8 grm. of dry faeces were taken for extraction, and in some cases mixed with sand, but neither this process nor the taking of smaller quantities (e.g. 2 or 3 grm. of dry material) was found to affect the result.

The neutral fat and fatty acids were estimated by extracting the dried faeces with dry ether in Soxhlet's apparatus. Triplicate determinations were made in most cases and duplicate in the others.

The extraction was continued for forty-eight hours; the extract, after distilling off the ether, was placed in the steam oven for one hour, cooled in the desiccator for one hour, and weighed. The neutral fat and fatty acids so obtained were dissolved in a mixture of alcohol and ether and titrated with half-normal alcoholic potash, using phenolphthalein as indicator. The fatty acids so determined were expressed as stearic acid.

The soaps in the residue were converted into fatty acids by wetting with alcohol, adding a few c.c. of 4 per cent. hydrochloric acid, mixing with water and testing to ascertain that the mixture was thoroughly acid. This was then dried on the water bath and finally in the steam oven, and the dry material transferred as quickly as possible, being very hygroscopic, to the Soxhlet thimble, placed in the oven again for a short time, and then extracted with dry ether for twenty-four hours. The extract was weighed and titrated as before, using one-fifth normal alcoholic potash. The titration values, expressed as stearic acid, were found to agree closely with the figures obtained by weighing.

The estimation of total fat with a Werner-Schmidt tube, making three extractions with ether and siphoning off practically the whole of the solvent each time, did not give results concordant with those obtained by the Soxhlet method. The figures were usually higher and in a variable degree. The determination of neutral fat and fatty acids by the same method was also found to be unsatisfactory in this case.

The nitrogen in the dried faeces was estimated by the Kjeldahl process, potassium permanganate being added to hasten oxidation.

Charcoal was given at the beginning and end of each diet period, to separate the stool corresponding to that period. As a rule, part of the charcoal appeared in the latter half of the motion passed after some twenty-six hours, the remainder in the first part of the following motion, about twenty-four hours later. The

earliest appearance was twelve hours, in which case it had all disappeared after thirty-six hours.

Carmine was not found satisfactory as a pigment in this case.

Quantity of Faeces.

Column 5 in Table II gives the average daily weight of faeces in each series of examinations.

TABLE II.

1	2	3	4	5	6	7	8
Series.	Periods.	Number of days.	Dates.	Wt. faeces. Mean per diem.	% water.	Total fat % in dry faeces.	Total fat excreted. Mean per diem.
I.	Prelim.	4	19–22 Dec., 1913	1224	60·2	62·6	302
II.	A–F	15	6–21 Jan., 1914	1040	64·1	58·9	233
III.	G–M	18	15 Feb.–4 Mar., 1914	981	66·1	54·1	180
IV.	P–U	15	between 29 Mar. and 18 Apr., 1914	813	64·9	59·1	170
V.	V–X	6	between 30 Mar. and 17 Apr., 1915	1216	61·5	58·2	261
	Whole series	58		994	64·4	57·7	207
	Highest figures } from different { Lowest figures } samples {			2649 331	68·1 59·1	66·9 48·9	339 75

The quantity passed per diem approximated to a kilogramme, that is, five times the amount passed by a healthy man. Frequently, especially in the earlier observations, stools were passed at twelve-hourly intervals, the average weight of successive stools often exceeding 700 grm. Later, one stool only was passed in twenty-four hours. The weight of the largest individual stool was 1,944 grm., the greatest amount of faeces passed in twenty-four hours being 2,649, a morning stool of 1,517 and an evening stool of 1,132, followed by one of 840 grm. the next morning. As the ash in the faeces was not above a normal amount and bacteria did not appear in great excess, the additional weight of the solid matter of the stools was due to excreted fat and nitrogenous substances.

The above table shows that the amount diminished greatly with treatment, falling from an average of 1,224 to 813 grm. This was due to less fat being lost because, as will be shown later, less non-emulsified fat was given in the food. When the dieting was not so careful the bulk of the stools increased again. Thus, on re-admission of the patient, a year later, stools were passed in the first week ranging in weight from 331 to 1,243 grm. averaging 1,384 grm. per diem, the largest amount passed in the twenty-four hours being 2,010 grm.

The reduction of the bulk of the faeces had alone a great effect on the well-being of the patient, who was tired out after the prolonged effort of passing such a large mass.

Total Quantity of Fat passed out.

The total fat in the faeces ranged from 75 to 339 grm. per diem, and varied, as appears later, with different circumstances, especially with the amount of fat in the food. Usually about 200 grm. per diem were passed out.

These figures are of the same order of magnitude as those reported by Vaughan Harley and Gross in similar cases, and by Deucher, and Brugsch and König in cases complicated with jaundice. The total amount of fat passed out in the first days of admission in Series I, namely 302 grm. per diem for four days, is the highest yet recorded, the next being Gross's first case, in which 208 grm. of fat per diem were lost in a two days' observation (18).

The percentage of fat in the dried faeces was correspondingly high, ranging from 49 per cent. to 67 per cent. The percentage does not appear to be affected by the nature or amount of the fat in the diet.

Percentages of 80 per cent. or more have been recorded in cases without and with obstructions of the bile duct—by Gross, Deucher, Garrod and Hurtley, and Cammidge.

Dr. Cammidge kindly informs us that the highest figure found by him in a case of uncomplicated pancreatic disease was obtained from this patient when under his care.

Whipple records 80 per cent. fat in the dry faeces in a case of a different nature.

The determination of the percentage of fat in the dried faeces is a comparatively simple matter, as only a sample of the motion is needed; but for purposes of diagnosis it is of greater value to ascertain the total amount of fat passed out per diem. This, however, has been comparatively seldom done.

A pathological excretion of fat by the intestinal mucous membrane has not been demonstrated to an extent of more than 8 grm. a day, an amount which in this case is negligible.

The loss of energy in the form of fat in the motions formed a large proportion—25 to 59 per cent. of the total caloric energy of the food, as is shown in the following table.

TABLE III.

| | DIET. | | FAECES. | |
Period.	Caloric value per diem.	Percentage of caloric energy due to fat in diet.	Caloric value of fat in faeces per diem.	Percentage energy lost by fat in faeces.
P	2816	45	698	25
M	3737	47	1163	31
R	4509	54	1721	38
T	4578	44	1814	40
G	3400	59	1395	41
W	4808	65	2026	42
Q	3676	47	1581	43
V	5307	65	2513	47
X	4678	59	2745	59

The mean loss of energy through unabsorbed fat for these twenty-three days

works out at 39·6 per cent. of the total in the diet ; the total loss of energy in the faeces was still greater owing to the loss of protein.

Absorption of Fat.

For the reasons given on p. 14, conclusions as to the relation between the amount of fat taken and that excreted are drawn from the 3rd, 4th, and 5th series of analyses.

TABLE IV.

1	2	3	4	5	6	
Period.	Number of days.	Fat in diet per diem.	Fat in faeces per diem.	% Fat absorbed.	% Fat lost in faeces.	
X	2	299	295	1	99	Pancreas
Q	3	186	170	9	91	No milk
T	2	217	195	10	90	Pancreas
V	2	369	270	27	73	No ferments
R	3	262	185	29	71	Much milk
G	3	217	150	31	69	No ferments
M	3	188	125	34	66	Skim milk
W	2	334	218	35	65	Trypsogen
P	3	136	75	45	55	Schmidt's diet

In Table IV the fat in the diet is compared with that in the faeces. In column 5, it is seen the percentage of fat absorbed was very low, ranging from 45 per cent. to only 1 per cent.

The maximum absorption of 45 per cent. resulted from a three days' trial of Schmidt's diet ; the healthy control, taking the same diet for the same period, absorbed 96 per cent. of the fat. As a general rule we have found that, in cases where the pancreas is not suspected, 90 per cent. or over of the fat in Schmidt's diet has been absorbed. We have found no case in the literature of pancreatic disease in which the absorption of fat has been so seriously affected.

The nearest approach is in a record of two cases of growth of the pancreas observed by Deucher ; in one of these only 17 per cent., in the other 47 per cent., of the fat given was absorbed, 83 per cent. and 53 per cent. respectively being lost in the faeces. Gross records a loss of over 50 per cent. of ingested fat. In two cases of Weintraud's the loss was 22 and 25 per cent. respectively.

Abelmann found that after removal of the pancreas dogs lost as much as 72 per cent. of ingested fat in the motions. (See also (8), (4), (30).)

Absorption of Fat with Variations of the Amount of Fat in the Food.

In a case of pancreatic disease observed by Gross, and in Garrod and Hurtley's case, it was found that when the amount of fat in the food was varied the percentage which was absorbed remained the same. Garrod and Hurtley suggest that such constancy of the percentage of fat absorbed, appears to indicate ' a deficiency of some agent which influences or controls fat absorption, rather

than a limitation of the absorptive power of the intestinal walls'. To test this point we may compare periods R and P; in each of these the nature of the fat was similar—36–44 per cent. being in the form of emulsified fat (milk), and 37–34 per cent. consisting of fat in butter and meat.   (Vide Table VI.)

TABLE V.

Period.	Fat in food per diem.	Percentage of fat absorbed.	Nature of fat in diet.
R 3 days	262	29	Emulsified fat in milk
P 3 days	136	45	Emulsified fat in milk. Schmidt's diet

It is seen that the percentage of fat absorbed was much less when a large quantity was given. This is confirmed by a consideration of several other periods, and is similar to that obtained in Gross's second case, in which, as in our own, the patient's nutrition was severely affected. Our patient's clinical state did not, however, vary in the different periods to such a degree as is described by Gross.

It is possible that a constant percentage of fat is absorbed in such cases when the patient's nutrition is good, but it is clear that no general rule or law can be laid down.

Effect of State and Nature of Fat.

(i) *Emulsified fat.*   Since Abelmann found that apancreatic dogs were able to absorb emulsified fats to some extent but not other fats, patients with deficient absorption have usually been given good quantities of milk. Brugsch, however, reports that in a man in whom no pancreatic juice passed into the intestine, milk was not better absorbed than non-emulsified fats.

In period R our patient was given 1,500 c.c. new milk, and 150 c.c. cream, whilst in period Q he took skim milk only, and no cream. In period P with Schmidt's diet, he was taking 1,500 c.c. new milk, and no cream.

TABLE VI.

1	2	3	4	5	6	7
	Percentage of Total Fat in Diet.					
Period.	In Milk. Emulsified fat.	In Cream.	In Butter.	Total emulsified fat.	Total fat derived from milk, cream and butter. (4 and 5)	Percentage of fat absorbed.
Q	2	0	54	2	56	9
R	23	13	37	36	73	29
P	44	0	34	44	78	45

It is seen that when a good quantity of fat was given in new milk, the absorption was at its best, reaching a higher figure than at any other period; it

was at its worst with skim milk and no cream, that is, when all the fat was in a non-emulsified form.

The increased absorption of fat from new milk is due to the emulsified state and not to the composition, for in period Q the same fats were being given in butter, as shown in column 6, but absorption was very poor.

The weight of the faeces was also naturally less when more fat was absorbed. Table VII shows that when milk fat was given, the ratio $\frac{\text{weight of dry faeces}}{\text{fat in diet}}$ was greatest in period Q, in which the milk fat was in a non-emulsified form, viz. butter.

TABLE VII.

1	2	3 Period.	4 Fat in diet.	5 Weight of faeces.	6 Weight of dry faeces.	7 Weight of dry faeces. (Ratio.) Fat in diet.
From lower melting fats chiefly	Emulsified fat	P	136	389	136	1·0
		R	262	862	308	1·2
	Non-emulsified fat	Q	186	819	290	1·6
From higher melting fats chiefly	Non-emulsified	V	369	1180	441	1·2
		G	217	782	277	1·3
		M	188	708	248	1·3

As regards the composition of the fat, when a diet containing fat of low melting-point, viz. butter, is compared with one containing the same amount of fat of higher melting-point derived from meat, it appears that the bulk of faeces was proportionately greater with butter fat. Butter fat did not in this case appear to be absorbed better than meat fat, as may be seen by comparing period Q with M in Table XVI, col. 14, p. 31.

This result was unexpected, as in health fats of low melting-points are said to be more completely absorbed than others (31).

To test this point further, 70 grm. per diem of cod-liver oil, which consists of low melting-point fats, was given for three days, the fat in this quantity amounting to 28 per cent. of the total fat in the diet. The subjective abdominal symptoms were worse and the exhausting motions larger and more frequent, containing a markedly higher percentage of water. It appeared that little, if any, of the oil was absorbed.

Fat-Splitting.

Much attention has been paid to the relative proportion of fat, fatty acid, and soap in the faeces, since Müller showed, in 1887, that in two cases of pancreatic disease, one of cyst and one of calculus, the lipolysis of the food fat in the intestine was interfered with, that is to say, a smaller proportion than usual of neutral fat was hydrolysed to form fatty acid or soap, owing presumably to absence of the lipolytic ferment, steapsin, of the pancreatic juice.

In the normal intestine about 75 per cent. of the fat is split to form fatty

acid or soap. As in biliary obstruction fat-splitting is not usually affected, these proportions became of diagnostic interest.

Weintraud and Katz published similar observations, and the view was expressed by the latter, that, if less than 70 per cent. of the fat were split, pancreatic disease should be suspected. This may be, but further observations have shown that the converse is not true, for fat may be split to a normal extent in pancreatic disorder.

Deucher found 80 per cent. and 92 per cent. and 62 per cent. split; Albu 80 per cent. to 90 per cent.; Ury and Alexander report that fat-splitting may be normal, or increased, or diminished in pancreatic disease; Keuthe had a case with 92 per cent. split, and Ehrmann found 57 per cent.; Gross, in his case II, found a loss of 80 per cent. fat, with 91 per cent. of it split; Przibram, and Cammidge also report varying figures, the average percentage of split fat in twenty cases diagnosed by the latter as cirrhosis of the pancreas being eighty-one, and in twenty-five cases with a diagnosis of catarrhal pancreatitis ninety-one per cent.

Similar variations have been found experimentally, the proportion of split fat in the stools of apancreatic dogs, ranging from 11 per cent. (16) and 30 per cent. (23) to normal figures (5) (23).

In this patient the amount of fat split varied from 80 per cent. to 94 per cent., the mean for 54 days being 87 per cent. In other words only 6 per cent. to 20 per cent. was present as neutral fat, as is shown in the following summary, extending over $8\frac{1}{2}$ weeks of analyses.

TABLE VIII.

No. of days.	Nature of diet.	Split fat.	Neutral fat.	Fatty acid.	Soap.	Fatty acids. (Ratio.) Soap.
		Per cent.	of Total	Fat.		
29	general	88·8	11·2	67·8	21·0	3·2
16	general (with panc. preparations)	84·5	15·5	66·7	17·8	3 8
3	fat in fat meat chiefly	93·9	6·1	71·2	22·7	3·1
3	mixed diet and cod-liver oil	80·2	19·8	77·0	3·2	24·0
3	Schmidt's diet	87·2	12·8	61·0	26·2	2·3

The figures for Series V (a year later) are similar :—

2	general	92·2	7·8	77·9	14·3	5·4
4	general (with panc. preparations)	84·5	15·5	72·5	12·0	6·0

It is seen that the proportion of fat split was greater than the normal.

It is evident that the deficiency of absorption is not due to deficiency of lipolysis, but ferment activities are so delicate that it is not justifiable to assume that when the fat is split by some other agent it is as suitable for absorption as when it is prepared by the normal activity of steapsin. Adding extract of pancreas from other animals to the food, although improving the absorption of nitrogen, as shown later, did not affect that of fat. It is not certain, however, that steapsin is offered to the small intestine in suitable form by this means, for

the fat-splitting ferment is the most difficult of the pancreatic ferments to prepare and to preserve. Even when fresh pancreas is given, only those zymogens or ferments which survive the gastric juice can be active in the intestine.

We do not know what agent splits fat in the absence of pancreatic juice. The gastric juice (38) (14), bile, and intestinal juice all possess lipolytic power, and it appears probable that they replace steapsin.

Brugsch found that fats were split normally in material collected from different parts of the alimentary canal of dogs, in which either the pancreas had been extirpated, or total atrophy induced by tying the vessels and ducts. He attributed the lipolysis to the remaining digestive juices.

In explanation of the varying proportions of split fat reported in pancreatic disease in man, Katz suggests that the fat-splitting is perhaps less disturbed when the onset of the lesion in the pancreas is gradual, as it most probably was in our patient.

Some writers regard bacteria as responsible for fat-splitting in the absence of pancreatic juice, but in Müller's experiments (1887) he was unable to get more than 9 per cent. to 13 per cent. fat split in vitro by bacterial action.

If bacterial action is important, it might be increased by a co-existent intestinal catarrh. There was not, however, such an excess of inorganic ash in this case as accompanies severe catarrh. The intestine was irritable, but probably this was a result of the acid reaction of the faeces, rather than a cause. The patient was more comfortable when less fat was contained in the diet and therefore less fatty acid present in the bowel.

Effect of Varying Quantities of Fat in Diet on Fat-Splitting.

When diets of closely similar composition but containing different quantities of fat are compared, no appreciable effect is traced upon the fat-splitting.

TABLE IX.

Period of diet.	Nature of fat.	Fat in food.	Split fat.
P	Schmidt's diet. Fat as milk and butter	136	87·2 %
R	Fat chiefly as milk and butter, but greater in quantity than in P	262	86·2 %

Effect of Form and Nature of Fat in Fat-Splitting.

In Table X the proportion of the total fat in the forms of milk, and cream, and of butter is given in periods P, R, Q, V, G, and M. It is seen that wide variation in the form of fat in the food is not accompanied by any appreciable alteration in the percentage of the fat which is split.

TABLE X. *Variation of Split Fat with Kind of Fat.*

Period.	Per cent. of Total Fat in Diet.			Split fat.	
	Fat in milk and cream. *a*	Fat in butter. *b*	Total. *a* and *b*	% total fat excreted.	
P	44	34	78	87·2	Schmidt
R	36	37	73	86·2	Skim milk
Q	2	54	56	86·4	Schmidt and extra milk
V	22	18	40	92·2	No milk
G	6	18	24	88·0	No milk
M	6	10	16	88·8	Diabetic diet

With cod-liver oil, forming 28 per cent. of the fat in the diet, the split fat was reduced to 80 per cent., the lowest figure obtained.   This is probably because the oil caused much looseness and passed quickly through the alimentary canal. There was a good deal of discomfort and a large bulk of faeces.   The proportion of neutral fat was accordingly greatest in this period.

It is seen later that with the ferments there was a tendency to a slight reduction of the fat split; this was, however, probably also due to the more rapid passage of the material through the intestine.

Proportion of Soaps.

Fat in the faeces which has been hydrolysed is in the form either of fatty acids or soaps.   In health, the quantity of each is nearly the same, there being usually a little more soap.

The proportion probably depends on the amount of alkali which is available for neutralizing fatty acids as they are formed.   In pancreatic disease the proportion of soap is often lower than normal, and this is ascribed to the absence of the alkali of the pancreatic juice.   Thus Hédon et Ville found that removal of the greater part of the pancreas in the dog after ligature of the bile duct led to disappearance of soaps from the faeces.   The fatty acids were diminished, but not greatly.   In our case the percentage of the fat of the faeces in the form of soaps, which is usually about 12 per cent., varied from 11·0 per cent. to 29·6 per cent., except with cod-liver oil, when the figure fell to 3·2 per cent. The ratio $\dfrac{\text{Fatty acid}}{\text{Soap}}$, which is usually a little less than unity, ranged from 2·3 to 4·5.

Comparative Figures.

In spite of the numerous figures in the literature, it may be of interest to mention the results of a series of estimations of the distribution of the fatty bodies in the faeces, made for diagnostic purposes in this laboratory in patients taking Schmidt's standard diet, the analytical methods used being the same in all respects as in this case.

In a healthy man 4·4 per cent. of the total fat in the diet was excreted—

containing neutral fat 53 per cent., fatty acids 34·1 per cent., soaps 12·8 per cent., and split fat 46·9 per cent. ; and in four other cases in which no disease of the pancreas was indicated the split fat ranged from 45 per cent. to 72 per cent. of the total fat excreted.

In dealing with healthy faeces, with low proportions of fat, it must be borne in mind that the experimental error in working with such small quantities becomes magnified in expressing results as percentages.

Nitrogen in Faeces.

The patient had accustomed himself to a modified diabetic diet for a considerable time, and was taking habitually large quantities of fat and protein.

We have mentioned above that undigested muscle fibres were abundant in the motions.

Estimation of the nitrogen showed about 5 per cent. in the dried material of the faeces, giving a total which varied from 14 to 23 grm. per diem, and on one day reached 30 grm.

A normal person on a mixed diet loses not more than 2 grm. in the day, or less than 10 per cent. of the total excretion of nitrogen. Even with a very large mixed diet, containing on the average 39 grm. of nitrogen, which was taken by a person suffering from no organic disease, only 1·6 grm. of nitrogen were found per diem in the faeces on the average (19). This was 4·15 per cent. of the ingested nitrogen and 6·01 per cent. of the total nitrogen recovered in the urine and faeces.

In this case, as is shown in the following table, 44 per cent. of the total nitrogen passed out was contained in the faeces.

TABLE XI.

Period.	Nitrogen in Diet.	Nitrogen excreted.		Nitrogen in faeces. % of total Nitrogen excreted.	Nitrogen in faeces. % of Nitrogen in diet.
		In Urine.	In Faeces.		
	grm. per diem.	grm. per diem.	grm. per diem.		
P	19·0	18·4	7·0	27·6	36·8
Q	26·1	16·6	14·3	46·4	54·8
R	27·7	14·5	14·2	49·6	51·3
T	35·5	23·5	17·2	42·3	48·5
M	37·0	26·1	15·4	37·0	41·6
G	38·4	25·2	15·7	38·4	40·9
W	46·2	20·9	22·8	52·2	49·3
X	49·3	21·8	22·8	51·2	42·6
V	53·6	24·8	29·5	54·3	59·8
Means of 9 above determinations	37·0	21·3	17·7	44·3	47·3
Means of all determinations *		23·6	19·0	44·0	
Number of determinations	9	17	25	17	9

* See Columns 20–26, Table XVI.

In the last column it is seen that 47 per cent. of the nitrogen in the diet was excreted in the faeces, indicating a wastage of practically this proportion of the protein given in the food.

Gross found a nitrogen loss in his two cases of from 30 per cent. to 50 per cent. in the stools, and in one metabolic period of two days the total nitrogen excreted showed a negative balance of 17·4 grm. Weintraud also found a loss of 61 per cent. nitrogen in the faeces. Morrison and Pratt report a loss of 51 per cent. in a patient with symptoms of obstruction of the pancreatic duct.

The figures are of the same magnitude as that found by Abelmann for the nitrogen wasted in the faeces of dogs deprived of the pancreas.

We have no data which tell us how much of the nitrogen in the motions was in the form of protein or of such of its derivatives as possess caloric energy, but we may assume that a great part was, the loss of which would detract materially from the energy furnished to the body.

This assumption is supported by the fact that when the fat and ash of the faeces are added to the nitrogen multiplied by 6·25, the sum arrived at is approximately equal to the weight of dried faeces. The following table shows three examples taken at random.

TABLE XII.

Period.	Fat.	Ash.	Nitrogen × 6·25	Fat + Ash + N × 6·25	Weight of dried faeces.	Difference.
		grm. per diem				grm.
G	150	19	98	267	277	−10
T	195	23	107	325	330	−5
V	270	34	143	447	441	+6

If all the nitrogen in the faeces was present as protein the loss of energy from this source would be approximately 10 per cent. of the total in the food.

TABLE XIII.

	DIET.		FAECES.	
Period.	Total caloric value per diem.	Percentage of caloric energy of diet due to protein.	Caloric value of nitrogen in faeces × 6·25	% loss of energy from 'protein' in faeces.
P	2816	17	179	6·4
R	4509	16	362	8·0
T	4578	20	440	9·6
Q	3676	18	365	10·0
M	3737	25	393	10·6
V	5307	26	585	11·0
W	4808	25	584	12·1
X	4678	27	756	16·2

Mean of 20 days: 10·1

The loss of energy due to the fat in the faeces on these same diets was 39·6 per cent., giving a total loss from fat and protein of about 50 per cent. of the energy of the food on the average. When the waste of carbohydrate as sugar

is also taken into account the total loss of energy from the food materials passed out in the faeces and urine varied from 32 per cent. to 62 per cent. of that in the food, and in one period (X) reached 85 per cent. This period was exceptional, however, for the reasons stated on page 27. Table XIV shows the proportionate loss of energy due to protein, carbohydrate, and fat for the highest and lowest values of the total loss.

TABLE XIV.

Period.	DIET.				Nitrogen in Faeces.	Sugar in Urine.	Fat in Faeces.	Percentage loss of energy.			
	Calories.	Protein.	Carbo-hydrate.	Fat.				'Protein' in Faeces.	Sugar in Urine.	Fat in Faeces.	Total.
P	2816	119	262	136	7.0	8.4	75	6	1	25	32
V	5307	335	55	369	21.8	41.0	270	11	3	47	61
X	4678	308	68	299	29.5	117.6	295	16	10	59	85

The difficulty of maintaining nutrition in these conditions is obvious.

In biliary obstruction, in which fat absorption is severely affected, the absorption of the nitrogen is usually normal or nearly so; neither does the ingestion of large quantities of fat affect the absorption of nitrogen in the healthy intestine. If the intestine is interfered with, however, the case may perhaps be otherwise, for in dogs deprived of the greater part of the small intestine the loss of nitrogen in the motions, 12 per cent., may be doubled by adding a large amount of fat to the food (12).

The digestion and absorption of protein can be improved in some cases by administering pancreatic ferments artificially. Thus Gross found that less nitrogen was lost when large quantities of pankreon were given. In this patient any beneficial effect was neutralized by the increased motions caused by irritation of the bowel.

Glycosuria.

In our case, as in others of a similar nature, the glycosuria, although often excessive, could be controlled. Thus on the first admission the patient was passing 79 grm. of sugar in the urine. With reduction of the carbohydrates in the diet the quantity fell until on the sixth day there was none, the patient still taking 70 grm. of carbohydrates in the food. It was fortunate that a tolerance for starches was easily re-established, for with so great a loss of fat and protein in the faeces, the best hope of restoring caloric equilibrium lay in improving the assimilation of carbohydrates. Accordingly the amount of starch in the food was gradually increased after the urine became sugar-free, until ultimately 370 grm. of starchy food, yielding over 1,500 calories, was being given per diem in the form of assimilable carbohydrate. The weight responded to this dietetic improvement, an increase of five pounds in one week being recorded at this time.

The 370 grm. of carbohydrate was given in the form of toast (44 per cent.), oatcake and porridge (23 per cent.), rice-pudding (5 per cent.), and potatoes (3 per cent.).

There is little doubt that a quiet, regular life had an influence in improving sugar assimilation.

On the second admission the sugar was also easily controllable. On a third admission, a year later, 466 grm. per diem were being passed. With restriction this quantity sank in six days to 11 grm., but the urine did not become entirely sugar-free for some weeks, even with a strict diet.

The power of assimilation had also fallen to some extent, and the patient had lost a stone in weight.

Pratt found glycosuria in six out of thirty-seven cases of pancreatic disease, and with 100 grm. of dextrose alimentary glycosuria occurred in four others of them.

Acidosis.

A trace of aceto-acetic acid was present in the urine on one day only, the second day of restriction of carbohydrate after admission.

Acetone was also found once in a quantity of 0·3 grm. in twenty-four hours, this occasion being on the first day of restriction to 56 grm. of carbohydrate. The urine contained 76 grm. of sugar. On the next day neither sugar nor acetone was present.

The urine quickly became alkaline when bicarbonate of soda was taken.

Acidosis was therefore but slight.

Administration of Ferments.

Fresh pig's pancreas, trypsogen, glycerine extract of pancreas, holadin, liquor pancreatis, papain, and pankreon were each given for periods of two or three days.

Fresh pancreas. Two periods are summarized in the following table, each being compared with a period without ferment in which the composition of the diet was similar. In both periods the absorption of fat was decreased while the fresh pancreas was being taken. The percentage of nitrogen absorbed was slightly increased in one period, but definitely less in the other (period X). During period X the patient was subjected to great anxiety about family affairs, which might explain the deficient absorption, but no such explanation can apply to period T.

TABLE XV.

1 Period.	2	3 No. of days.	4 Wt. of faeces.	5 % water in faeces.	6 Wt. of fat in diet.	7 Wt. of fat in faeces.	8 % of food fat lost in faeces.	9 Split fat % of total fat.	10 Nitrogen in diet.	11 Nitrogen in urine.	12 Nitrogen in faeces.	13 % of food N. lost in faeces.
T	Fresh pancreas 42 grm. per diem	2	995	66·8	217	195	90	82·6	35·5	23·5	17·2	49
R	Diet similar to T, but without ferment	3	862	64·3	262	185	71	86·2	27·7	14·5	14·2	51
X	Fresh pancreas 42 grm. per diem	2	1452	66·3	299	295	99	85·6	49·3	24·8	29·5	60
V	Diet similar to X and W, but without ferment	2	1180	60·5	369	270	73	92·2	53·6	21·8	22·8	43
W	Trypsogen 12 tablets per diem	2	1015	59·1	334	218	65	83·4	46·2	20·9	22·8	49

Figures in Columns 4, 6, 7, 10, 11, 12 refer to grm. per diem.

Trypsogen. Four tablets were given three times a day during the experimental period (W), the preparation having been given for the three preceding days in increasing amount. An increased absorption of fat resulted, viz. 8 per cent., a third more than when no trypsogen was included in the diet. The bulk of the faeces was also reduced by 10 per cent. The amount and nature of fat in the diet were practically the same in the two periods. The absorption of nitrogen was less.

Other ferments. A glycerin extract of fresh pancreas was made as follows: a perfectly fresh pig's pancreas was freed from fat, weighed, finely minced, and ground with sand. It was extracted for twenty-four hours with a mixture consisting of 90 parts of pure glycerin and 10 parts of 1 per cent. sodium carbonate solution, 10 c.c. of the mixture being taken for every gramme of pancreas. The fluid was then strained through muslin. The extract was given in 4 c.c. doses thrice daily in period H.

In period J one capsule of holadin, in period L 4 c.c. of liquor pancreatis, and in period S 0·7 grm. of papain was given three times a day after food.

In period V ten tablets of powdered pankreon were given four times a day after food, that is, 10 grm. of pankreon in the day, this being the dose which Gross found effective in improving the absorption of nitrogen.

In periods H, J, L, and S, the diet was controlled daily, but for reasons already given the figures are not inserted in the analytical figures. In H, J, and L the fat in amount and composition was similar to that in the diet in period Q. In S (and V) the diet resembled that of period R.

The analytical figures will be found in Table XVI, pp. 30–3. They show that with all these ferments except trypsogen the bulk of faeces was increased, especially with the glycerin extract of pancreas, holadin, and papain. The fat absorption was not improved. When the fat in the faeces is compared with that in the diet, even allowing for a wide margin of error, it appears that with holadin, liquor pancreatis, papain, and pankreon, less fat was absorbed than in the control periods.

The absorption of nitrogen appeared on the whole to be slightly improved. In the case of pankreon the improvement was well marked, estimation of the protein in period U showing that the proportion of nitrogen lost was less than 30 per cent.

All these ferments except fresh pancreas and trypsogen irritated the intestinal tract and caused the patient serious discomfort.

The increased rate of passage of material appeared to be responsible for the deficient absorption of fat in this case. Probably much better results, such as are reported by others, would have been obtained had the intestine been less irritable.

A comparison of the figures for split fat in these periods show that lipolysis was not much affected. On the average the proportion of fat split was 2 or 3 per cent. less than when no ferment was given.

Summary.

1. A patient with the symptoms of chronic disease of the pancreas was under observation for 21 weeks, in five periods extending over 18 months. The urine and faeces were analysed for 64 days, and compared with the intake of food.

2. Trypsin could not be detected in the faeces and Sahli's capsules were not digested.

Diastase was present in the urine in normal amount.

3. An average of 1,200 grm. of faeces was passed in a day on admission. With the reduction of unassimilable forms of fat in the food the quantity was reduced to 800 grm. in the first period of treatment, much to the comfort of the patient.

4. An average of 302 grm. of fat per day was lost in the motions on admission. This is higher than in any other case we have found recorded. From 25 to 59 per cent. of the caloric energy of the food was lost in this way.

5. The proportion of fat in the food which was lost in the faeces varied from 55 to 99 per cent. The emulsified fat of milk was much better absorbed than the fat of butter, meat, or cod-liver oil. The percentage absorbed was less when a large quantity of fat was given.

6. The proportion of the total fat in the faeces which had been split, and was in the form of fatty acids and soaps, was rather more than is normal throughout, the average of 54 days' figures being 87 per cent. Variations in the quantity and nature of the fat did not affect fat-splitting appreciably.

7. Nearly half the nitrogen of the food appeared in the faeces.

8. Sugar was present in the urine. At first it soon disappeared with suitable food, but each time the patient came under treatment a longer period on a restricted diet was required before the urine became sugar free. In the intervals of treatment unsuitable food was eaten.

9. There was no evidence of acidosis.

10. Various ferments were used in experimental periods. All except fresh pancreas and trypsogen irritated the intestinal tract. With trypsogen there was improvement in the absorption of fat, and with pankreon improvement in the absorption of nitrogen.

11. The general condition of the patient improved considerably with each period of rest and treatment.

TABLE XVI.

Period.	Number of Days.	Dates.	Calories.	Protein. grm.	Carbo-hydrate. grm.	Fat. grm.	Remarks.	Weight Aver. per diem. grm.	% Water.	Weight of Dry Matter Aver. per diem. grm.
1	2	3	4	5	6	7	8	9	10	11
					Averages per diem.					

Series I. (Preliminary.)

		1913								
i	1	18 Dec.	—	—	69	—		1335	60·9	522
ii	1	19 ,,	—	—	70	—	Diabetic	1155	61·1	449
iii	1	20 ,,	—	—	70	—	Diet	1022	59·9	409
iv	1	21 ,,	—	—	68	—		1384	59·1	567

Series II.

		914								
A	3	7–9 Jan.	—	—	—	—	The faeces were collected	1145	64·8	403
B	3	10–12 ,,	—	—	—	—	for a definite number of	1058	60·8	414
C	3	13–15 ,,	—	—	—	—	days in this Series (II).	1168	62·9	434
D	3	17–19 ,,	—	—	—	—	In subsequent Series (III	1166	65·1	406
E	2	20, 21 ,,	—	—	—	—	to V) faeces correspond	940	64·7	332
F	1	22 ,,	—	—	—	—	to definite diets	760	66·4	255

Series III.

G	3	15–17 Feb.	3400	241	70	217	No ferment preparations	782	64·6	277
H	3	18–20 ,,	—	—	97	—	Pancreas (Glycerin extract)	1037	65·1	362
J	3	21–23 ,,	—	—	160	—	'Holadin'	1124	67·4	367
K	3	24–26 ,,	—	—	186	—	Cod-liver oil	1270	68·1	405
L	3	27–1 Mar.	—	—	227	—	Liquor Pancreatis	965	66·5	324
M	3	2–4 ,,	3737	231	226	188	No ferments	708	65·0	248

Series IV.

P	3	29–31 Mar.	2816	119	262	136	Schmidt's Diet	389	65·0	136
Q	3	1–3 Apr.	3676	163	274	186	No emulsified fat	819	64·5	290
R	3	4–6 ,,	4509	173	298	262	Much emulsified fat	862	64·3	308
S	2	12, 13 ,,	—	—	306	—	'Papain'	1035	64·3	369
T	2	15, 16 ,,	4578	222	373	217	Fresh pancreas	995	66·8	330
U	2	17, 18 ,,	—	—	349	—	'Pankreon'	963	65·1	336

Series V.

		1915								
V	2	30, 31 Mar.	5307	335	55	369	No ferments	1180	60·5	441
W	2	10, 11 Apr.	4808	289	59	334	Trypsogen	1015	59·1	416
X	2	16, 17 ,,	4678	308	68	299	Fresh pancreas	1452	66·3	548

Analytical Figures.

Period.	12	13	14	15	16	17	18	19
				FAT IN FAECES.				
	% Fat in dried faeces.	Total Fat excreted. Aver. per diem (grm.)	% Loss of Food Fat in Faeces.	Split Fat.	Neutral Fat.	Fatty Acids.	Soaps.	Number of Determinations.
					Percentage of Total Fat.			

Series I.

Period.	12	13	14	15	16	17	18	19
i	63·6	330	—	97·9	2·1	69·5	28·4	2
ii	66·9	300	—	95·3	4·7	71·1	24·4	2
iii	58·4	238	—	84·4	15·6	63·0	21·4	2
iv	60·3	339	—	90·2	9·8	75·7	14·5	2

Series II.

Period.	12	13	14	15	16	17	18	19
A	59·7	240	—	91·9	8·1	70·9	21·0	2
B	66·0	274	—	91·2	8·8	67·9	23·3	3
C	66·0	286	—	83·1	16·8	65·0	18·2	2
D	53·9	219	—	91·8	8·2	71·0	20·8	2
E	49·1	163	—	93·9	6·1	71·2	22·7	2
F	48·9	125	—	89·9	10·1	71·1	18·8	4

Series III.

Period.	12	13	14	15	16	17	18	19
G	54·1	150	69·0	88·0	12·0	65·3	22·7	3
H	55·8	202	—	81·3	18·7	63·6	17·7	3
J	53·9	197	—	82·3	17·7	66·5	15·8	3
K	58·6	238	—	80·2	19·9	76·7	3·2	2
L	51·9	168	—	84·9	15·1	68·3	16·6	3
M	50·6	125	66·5	88·8	11·2	72·1	16·7	2

Series IV.

Period.	12	13	14	15	16	17	18	19
P	55·2	75	55·1	87·2	12·8	61·0	26·2	3
Q	58·8	170	91·4	86·4	13·6	64·2	22·2	3
R	60·0	185	70·7	86·2	13·8	70·4	15·8	3
S	59·7	220	—	87·4	12·6	65·4	22·0	3
T	59·2	195	90·0	82·6	17·4	65·8	16·8	3
U	63·1	212	—	88·6	11·4	69·7	18·9	3

Series V.

Period.	12	13	14	15	16	17	18	19
V	61·3	270	73·2	92·2	7·8	77·9	14·3	2
W	56·1	218	65·2	83·4	16·6	70·3	13·1	2
X	57·3	295	98·8	85·6	14·4	74·6	11·0	2

<div align="right">TABLE XVI</div>

Period.	NITROGEN.							ASH IN FAECES.	
	20	21	22	23	24	25	26	27	28
	Nitrogen in Urine.	Nitrogen in Faeces.	Total Nitrogen excreted.	Nitrogen in Diet.	Nitrogen Balance.	Nitrogen in Faeces % of Total Nitrogen excreted.	Nitrogen in Faeces % of Nitrogen in Diet.	% Ash in Dried Faeces.	Total Ash. Aver. per diem. grm.
	Averages per diem (grm.).				grms.				
Series 1.									
i	25·6	22·7	48·3	—	--	47·0	—	5·1	26·5
ii	—	20·5	—	—	—	—	—	5·8	26·2
iii	—	18·4	—	—	—	—	—	5·4	22·0
iv	26·5	25·9	52·4	—	—	49·5	—	6·4	36·4
Series II.									
A	—	17·5	—	—	—	—	—	5·3	21·4
B	—	19·7	—	—	—	—	—	5·4	22·4
C	—	19·4	—	—	—	—	—	4·4	18·4
D	—	23·4	—	—	—	—	—	5·9	23·8
E	—	20·8	—	—	—	—	—	4·7	15·6
F	—	15·3	—	—	—	—	—	5·8	14·7
Series III.									
G	25·2	15·7	40·9	38·4	-2·5	38·5	40·9	6·8	18·8
H	29·7	20·0	49·7	—	—	40·3	—	7·9	28·7
J	31·5 *	21·3	52·8	—	—	40·5	—	6·3	23·1
K	27·9	21·0	48·9	—	—	43·0	—	5·9	23·8
L	23·5 *	18·8	42·3	—	—	44·5	—	6·8	22·0
M	26·1 *	15·4	41·5	37·0	-4·5	37·0	41·6	4·8	11·9
Series IV.									
P	18·4	7·0	25·4	19·0	-6·4	27·6	36·8	—	—
Q	16·6	14·3	30·9	26·1	-4·5	46·4	54·8	7·1	20·6
R	14·5	14·2	28·7	27·7	-1·0	49·6	51·3	7·0	21·5
S	21·7	18·0	39·7	—	—	45·4	—	7·5	27·7
T	23·5	17·2	40·7	35·5	-5·2	42·3	48·5	6·7	22·3
U	23·3	14·3	37·6	—	—	38·0	—	7·2	24·1
Series V.									
V	21·8	22·8	44·6	53·6	+9·0	51·2	42·6	7·7	33·7
W	20·9	22·8	43·7	46·2	+2·6	52·2	49·3	7·1	29·4
X	24·8	29·5	54·3	49·3	-5·0	54·3	59·8	8·0	44·1

* Nitrogen in urine estimated on 2 out of 3 days in these periods.

(8

(*continued*).

Period.	CARBOHYDRATE				ENERGY					
	29	30	31	32	33	34	35	36	37	38
	Volume of Urine. c.c.	Sugar in Urine. grm.	Carbo-hydrate in Diet. grm.	% Carbo-hydrate assimi-lated.	Loss of Energy in Calories.				Energy in Diet. Calories.	% Loss of Energy.
					as Fat in Faeces.	as Pro-tein in Faeces.	as Carbo-hydrate in Urine.	Total Loss.		
	Averages per diem.				Averages per diem.					
Series I.										
i	3280	0	69	100	3069	582	0	3651	—	—
ii	3330	0	70	100	2790	525	0	3315	—	—
iii	3110	0	70	100	2214	472	0	2686	—	—
iv	3100	0	68	100	3153	664	0	3817	—	—
Series II.	*	*	*							
A	2800	38·1	110	65	2232	448	156	2836	—	—
B	3110	0	104	100	2548	505	0	3053	—	—
C	2630	0	63	100	2660	497	0	3157	—	—
D	2830	0	83	100	2037	600	0	2637	—	—
E	3120	0	88	100	1516	533	0	2049	—	—
F	3250	0	65	100	1163	392	0	1555	—	—
Series III.										
G	3030	0	70	100	1395	403	0	1798	3400	52·9
H	3060	0	97	100	1879	513	0	2392	—	—
J	3160	0	160	100	1832	546	0	2378	—	—
K	2475	0	186	100	2214	538	0	2752	—	—
L	2445	12·2	227	95	1562	482	50	2094	—	—
M	2670	0	226	100	1163	395	0	1558	3737	41·7
Series IV.										
P	1930	8·4	262	97	698	179	34	911	2816	32·4
Q	2430	2·5	274	99	1581	366	10	1957	3676	53·2
R	2790	0	298	100	1721	364	0	2085	4509	46·2
S	3075	4·6	306	99	2046	461	19	2526	—	—
T	3430	6·1	373	98	1814	441	25	2280	4578	49·8
U	3115	21·4	349	94	1972	366	88	2426	—	—
Series V.										
V	2980	41·0	54·5	25	2513	585	168	3266	5307	61·6
W	2890	59·6	59·4	0	2026	584	244	2854	4808	59·4
X	3755	117·6	68·2	0	2745	756	482	3983	4678	85·2

* These figures in Series II taken from urine and diets to which faeces correspond approximately. (See Column 8.)

TABLE OF

1	2	3	4	
		Faeces.		
Author and Date of Paper.	Diagnosis.	Naked Eye Characters.	Microscopic Characters.	

GROUP I.   *Diseases of the Pancreas*

I A.   *Cases in which the total fat per diem*

Vaughan Harley, 1896	Closure of pancreatic duct	Light-brown, foul, soft, oily	... ...	2
Ury and Alexander, 1904 Case II	Cancer of pancreas	First part—fluid fat	Numerous muscle fibres	
Case IV	Catarrh of pancreatic duct ?	Large, fatty, rancid, semi-solid, grey	... ...	
Glaessner und Sigel, 1904	Atrophy of pancreas	Large, 600–750 grm. per diem. Clear yellow, porridge-like, containing much fat which congealed. Acid. Odour of fatty acids	Abundant drops, flakes, and fatty acid crystals; large masses of intact muscle fibres. Some starch grains	6 3 3 3 3 3 ? 3 ? 3 ?

N.B.—Pankreatin and sodium bicarbonate gave the most favourable result both on the absorption of fat and protein

PUBLISHED ANALYSES.

5	6	7	8	9	10	11	12	13	14	15
Number of Days.	Total Fat excreted per diem.	Total Fat in Food per diem.	% Food Fat lost in Faeces.	% Food Nitrogen lost in Faeces.	% Fat in dried Faeces.	Split Fat.	Neutral Fat.	Fatty Acids.	Soaps.	Remarks.
							Percentage of Total Fat.			

without Biliary Complications.

in the food and faeces was estimated.

5	6	7	8	9	10	11	12	13	14	15
2	144	197	73·1	40	—	55·7	37·5	40·4	15·3	2nd and 3rd of 4 days' observation on milk diet. (Bile acids and bilirubin in faeces) 6·7 % cholesterin each day in dried faeces
—	—	—	72	40	—	—	—	—	—	Melting-pt. of faecal fat 24°–30° C.
—	46·6	80	58·3	—	51·7	—	—	—	—	At beginning of illness. Aet. 7 years
—	9·6	—	—	—	21·8	—	—	—	—	6 months later. (8 years later weak, thin but tall)
6	—	189	56	41	—	—	—	—	—	Initial period
3	—	189	62	35	—	—	—	—	—	Pankreon 5 grm. per diem
3	—	189	50	45	—	—	—	—	—	Final period
3	—	189	49	46	—	—	—	—	—	Initial period
3	—	189	97	75	—	—	—	—	—	Thyreoidin 1·5 grm. per diem (Diarrhoea)
3	—	189	55	49	—	—	—	—	—	Final period
	—	189	55	49	—	—	—	—	—	Initial period
3 ?	—	189	49	39	—	—	—	—	—	Sodium bicarbonate 30 grm. per diem
	—	189	52	45	—	—	—	—	—	Final period
	—	189	56	46	—	—	—	—	—	Initial period
3	—	189	41	42	—	—	—	—	—	Pankreon 5 grm. and sod. bicarb. 30 grm. per diem
	—	189	60	47	—	—	—	—	—	Final period
	—	182	59	48	—	—	—	—	—	Initial period
3 ?	—	182	31	43	—	—	—	—	—	Pankreatin 1·25 grm. per diem
	—	182	56	47	—	—	—	—	—	Final period
	—	191	62	47	—	—	—	—	—	Initial period
3 ?	—	191	30	38	—	—	—	—	—	Pankreatin 1·25 grm., and sod. bicarb. 30 grm. per diem
	—	191	56	48	—	—	—	—	—	Final period

1		2	3	4	5
Author and Date of Paper.		Diagnosis.	Faeces.		Number of
			Naked Eye Characters.	Microscopic Characters.	

GROUP I. *Diseases of the Pancreas*

I A. *Cases in which the total fat per diem*

Author and Date of Paper.		Diagnosis.	Naked Eye Characters.	Microscopic Characters.	
Keuthe, 1909		Calculi of pancreas. Atrophy *Autopsy*	'Diarrhoea'	... ...	—
O. Gross, 1912	Case I	Disease of Pancreas	Severe diarrhoea	... ...	2 2 2
					2
					2 2
					2
Normal Man		Control to above (Case I) and on same diet as in 2nd observation			2
	Case II	Disease of Pancreas			2
					2 2
					2
Morrison and Pratt, 1912		Obstruction of pancreatic ducts	... ...	... ...	—

I B. *Cases in which the total fat per diem*

Müller, 1887	Case I	Cyst of pancreas *Laparotomy*	Soft; 'brown-grey'	Muscle fibres with cross striation; few fat crystals	1 1
	Case III	Calculi of pancreas. Atrophy *Autopsy*	Large, foamy, foul, yellow	... ...	
v. Noorden, 1890		Degeneration of pancreas	... ...	... ...	—

5	6	7	8	9	10	11	12	13	14	15
Number of Days.	Total Fat excreted per diem.	Total Fat in Food per diem.	% Food Fat lost in Faeces.	% Food Nitrogen lost in Faeces.	% Fat in dried Faeces.	Split Fat.	Neutral Fat.	Fatty Acids.	Soaps.	Remarks.
						Percentage of Total Fat.				

without Biliary Complications (continued).

in the food and faeces was estimated (continued).

5	6	7	8	9	10	11	12	13	14	15
—	—	—	9·8	—	—	92	8	—	—	Transient glycosuria
2	208	375	55·4	50·8	—	61·3	38·7	56·8	4·5	Fat rich diet. Acidosis
2	44	84	52·4	51·2	—	65·5	34·5	61·6	3·9	Fat poor diet
2	104	165	62·9	—	—	88·0	11·9	82·9	5·1	Milk diet. When butter replaced part of milk fat absorption reduced to 56 % of which 81 % was split
2	153	295	52	52·8	—	68·7	31·4	66·5	2·2	Pankreon. 20 tablets = 5 grm.
2	124	225	55	{29·9 / 12·1}	—	70·3	30·0	53·1	17·2	Pankreon. 40 tablets = 10 grm.
2	123	226	54·5	28·5	—	78·8	22·3	70·0	8·8	Fresh pancreas of pig 75 grm.
2	106	219	56·4	16	—	76·1	23·3	73·9	2·2	Fresh pancreas of pig 75 grm.
2	2	84	2·5	—	—	64·5	35·4	52·4	12·1	Fat poor diet as in Case I (Gross)
2	55	208	26·2	{31 / 40}	—	92·1	7·8	82·8	7·8	1st observation. 40 % nitrogen lost on nitrogen rich diet
2	61	208	29·5	36·5	—	87·5	12·4	78·4	9·1	2nd observation
2	208	256	81	60	—	91·2	8·9	89·2	2·0	Exacerbations with severe diarrhoea
2	215	262	82·2	61·9	—	93·7	6·2	92·5	1·2	Pankreon. 20 tablets = 5 grm.
—	—	—	59	51	—	—	—	—	—	

in the food and faeces was not estimated.

5	6	7	8	9	10	11	12	13	14	15
1	—	—	—	—	30·8	48·8	51·2	—	—	Milk 2 litres; bread and meat
1	—	—	—	—	28·7	47·7	52	30·9	16·8	Mixed diet. With Schmidt's test, nuclei found intact
—	—	—	—	—	29	22	78	17	5	Glycosuria
—	—	—	—	—	29–30	23-29	—	—	—	

1	2	3	4
		Faeces.	
Author and Date of Paper.	Diagnosis.	Naked Eye Characters.	Microscopic Characters.

GROUP I. *Diseases of the Pancreas*

I B. *Cases in which the total fat per diem*

Ury and Alexander, 1904	Case I	Cancer of stomach and head of pancreas Tail of pancreas fatty and fibrous *Autopsy*	Large, fluid, yellow. Two layers; upper like butter	Numerous muscle fibres
	Case III	Tumour of pancreas	Fatty; semi-solid	Numerous muscle fibres
	Case V	Calculus of pancreas	Semi-solid	Very large number of muscle fibres
	Case VI	Disease of pancreas	Large, solid, grey	Numerous muscle fibres and fatty acid crystals
	Case VII	Disease of pancreas	Large and fatty. Sometimes fat only	Numerous muscle fibres and fat droplets
Atkinson and Hirsch, 1907		Calculi of pancreas. Fibrosis *Autopsy*	Large, fatty, rancid	Fat, muscle fibres, débris
Cammidge, 1914		Cirrhosis of pancreas Catarrhal pancreatitis	... ...	... ...

GROUP II.

Garrod and Hurtley, 1913	Case of congenital steatorrhœa	Large, fatty, rancid, sometimes liquid fat	Fat globules, fatty acid crystals, no muscle fibres or starch Micro-organisms chiefly Gram-negative
	Control to above on fat rich diet	... ...	... ...

5	6	7	8	9	10	11	12	13	14	15
Number of Days.	Total Fat excreted per diem.	Total Fat in Food per diem.	% Food Fat lost in Faeces.	% Food Nitrogen lost in Faeces.	% Fat in dried Faeces	Split Fat.	Neutral Fat	Fatty Acids.	Soaps.	Remarks.
						Percentage of Total Fat.				

without Biliary Complications (continued).

in the food and faeces was not estimated (continued).

5	6	7	8	9	10	11	12	13	14	15
—	—	—	—	—	—	9	91	—	—	
—	—	—	—	—	63	89·5	10·5	33·4	56·1	
—	—	—	—	—	25	59·4	40·6	33·8	25·6	
—	—	—	*	—	43·1	86·7	13·3	64·4	22·3	* 'At least 50 % fat unabsorbed'
—	—	—	—	—	29·0	47·7	52·2	32·6	15·1	
—	—	—	—	—	54·6	77·5	22·5	32·1	45·4	Glycosuria
—	—	—	—	—	26·5	80·8	19·2	42·3	38·5	Average of 20 cases
—	—	—	—	—	23·5	91·1	8·9	31·5	59·6	Average of 25 cases

GROUP II.

5	6	7	8	9	10	11	12	13	14	15
1	4·6	—	—	—	44	45·2	54·7	35·2	10·0	Almost fat free diet
4	23·8	92	25·9	—	55·5	68·0	32·0	45·5	22·5	Fat poor diet
9	42·6	177	24·0	—	79·4	38·6	61·4	32·6	6·0	Fat rich diet
5	54·5	177	30·8	—	83·4	60·1	39·8	52·0	8·2	Fat rich diet with Fel. Bov. (green)
6	42·2	177	23·8	—	77·1	34·2	65·8	28·6	5·6	Fat rich diet with Fel. Bov. (brown)
4	50·7	177	28·7	—	82·2	36·6	63·4	31·4	5·2	Fat rich diet with Glyco-cholate
1	79·3	177	44·8	—	87·5	55·9	44·1	55·3	0·6	Fat rich diet with Pan-kreon
1	95·6	177	54·0	—	83·0	68·1	31·9	57·8	10·3	Fat rich diet with Holadin
3	1·4	177	0·8	—	14·5	47·9	52·1	24·0	23·9	Fat rich diet

1		2	3	4
Author and Date of Paper.		Diagnosis.	Faeces.	
			Naked Eye Characters.	Microscopic Characters.

GROUP III. *Diseases of the Pancreas*

III A. *Cases in which the total fat per diem*

Deucher, 1898	Case I	Cancer of pancreas. Dilated duct. Atrophy. Recent implication of bile duct *Autopsy*	Colourless ...	... ...
	Case II	Cicatrix of duodenal ulcer obstructing pancreatic duct and (partly) bile duct	Large ; clay-coloured	Fatty acid crystals
	Case III	Tumour of pancreas closing pancreatic and bile ducts *Laparotomy*	'Colourless and clay-like'	... ...
Normal Man		... ...	... ...	... ...
Weintraud †, 1898	Case I	Cancer of pancreas. Jaundice	† N.B.—Original paper not accessible. Quoted from v. Noorden, *Pathology of Metabolism*, 1907, ii. 200 et seq.	
	Case II	Cancer of duodenum. Jaundice	... ...	... ...
Brugsch and König, 1905		Abcess of pancreas. Jaundice *Laparotomy*	... ...	... ...
Ehrmann, 1910	Case I	Obstruction of pancreatic duct. Gallstones *Laparotomy*	Large, fatty, rancid, butter-like, acid	Numerous muscle fibres and fat droplets. No starch
Spooner and Pratt, 1912		Cancer of pancreas. Jaundice	... ...	... ...

III B. *Cases in which the total fat per diem*

Müller, 1887	Case II	Duct of pancreas blocked with plug of mucus. Bile ducts dilated. Jaundice *Autopsy*	'Silver-white'	Feathery fine crystals. No excess muscle fibres. No starch granules
Cammidge, 1914		Stones in common bile duct. Jaundice	... ...	... ...
		Cancer of pancreas. Jaundice	... ...	... ...

5	6	7	8	9	10	11	12	13	14	15
Number of Days.	Total Fat excreted per diem.	Total Fat in Food per diem.	% Food Fat lost in Faeces.	% Food Nitrogen lost in Faeces.	% Fat in dried Faeces.	Split Fat.	Neutral Fat.	Fatty Acids.	Soaps.	Remarks.
						Percentage of Total Fat.				

with implication of the Bile Duct.

in the food and faeces was estimated.

5	6	7	8	9	10	11	12	13	14	15
2	59·2	71·4	83	30	—	80·4	19·6	73·3	7·1	1 litre milk and 8 eggs per diem. Occasional glycosuria. No jaundice, or bile in urine.
3	49·3	254	19·4	2	—	92·2	7·8	49·6	42·6	Mixed diet. Transient glycosuria
3	108·1	203·7	53·1	19·3	—	61·6	38·4	52·1	9·5	No meat in diet
—	—	—	3·1	1·8	—	77·7	22·3	32·6	45·1	Same diet as Case III ?
—	—	—	22·2	42*	—	23	77	—	—	* Pratt quoting this case (*Am. Journ. Med. Sc.*, 1912, 143) gives loss of nitrogen 61 %.
—	—	—	25·2	46*	—	27	73	—	—	Split fat figures from Müller
1	29·2	49	59·7	—	—	—	—	—	—	Stage I without jaundice
1	36·8	51	72·2	—	—	—	—	—	—	Stage II some jaundice
1	37·6	144	26·1	—	—	—	—	--	—	Stage III after Laparotomy. (Weight increased 25–30 lb. in 3 months following operation)
3	98	195	50·2	42·8	—	56·8	43·2	42·1	14·8	Case I without ferment
3	18	195	9·4	19·7	—	71·0	29·0	26·0	45·0	Control without ferment
3	53	195	27·2	17·0	—	61·6	38·4	30·8	30·8	Case I with Pankreatin (25 grm. per diem)
3	24	95	2·2	16·2	—	70·8	29·2	28·8	42·0	Control with Pankreatin (25 grm. per diem)
—	—	—	80	35	—	—	—	—	—	

in the food and faeces was not estimated.

5	6	7	8	9	10	11	12	13	14	15
—	—	—	—	—	43·9	49	51	22	27	Drops of fat in all of small intestine, crystals appeared first after ileo-caecal valve
—	—	—	—	—	57·1	92·5	7·5	38·4	54·1	Average of 36 cases
—	—	—	—	—	64·6	95·2	4·8	34·1	61·1	Average of 16 cases

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RESEARCHES ON THE PERFUSED HEART

SOME OBSERVATIONS ON THE CARDIAC RESERVE

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Introductory.

MACKENZIE (18) has divided the force inherent in cardiac muscle into two parts, the rest force employed to maintain the circulation when the body is at rest, and the reserve force called into action when effort is made. He also states that physiologists have not given the reserve force that study which its importance demands.

In a number of papers published by myself (2–15), however, various observations on this point have been given, but as each individual observation has formed part of material directed to other ends they may be regarded as adumbrations rather than as attempts at elucidation of the present problem. Accordingly, I have endeavoured to collect together such of them as seemed pertinent to the problem of the cardiac reserve, and combined them with new material. They indicate the solution to lie in the variations of the cardiac response to calcium.

It will be shown that the sum-total of the contractile material of the heart can be directly estimated apart from its spontaneous manifestations of activity, and that the proportion of that whole thrown into spontaneous contractile activity by a given tension of calcium varies with certain internal cardiac changes, elsewhere suggested to be the state of aggregation of certain cardiac colloids (5) (6).

Method of experiment. The methods have been carried out chiefly on the hearts of rana temporaria perfused, sometimes through the inferior vena cava, sometimes through the anterior abdominal vein.

Results. Not infrequently the two muscular functions of excitability and contraction are confused, and attention may be drawn first to the differentiation that may be made between them. The confusion depends to some extent on the use of the contractile response of a muscle on its excitation by an induced shock as a test of its contractility. The evidence is not altogether adequate, however, because muscles which do not contract in response to induced shocks may do so if some other agency be employed. For example, they may enter into rigor. Or,

as shown by Ioteyko (16), the galvanic current then excites contraction, and so on. Ioteyko, indeed, drew the conclusion from her experiments that two forms of contractile material existed in muscle, the one reacting to induced and the other to galvanic currents. She believed that the material which contracted in response to excitation by induced shocks had lost its contractility when those same shocks failed to evoke contraction.

But, in a paper published elsewhere, I showed that certain agencies evoked contraction from muscle at the expense of the material on which it draws when it contracts in response to induced shocks, and that those agencies might evoke undiminished contraction from muscles previously rendered inexcitable to induced shocks. A muscle may thus possess an undiminished store of contractile material at a time when the ordinary induced shocks fail to elicit contraction.
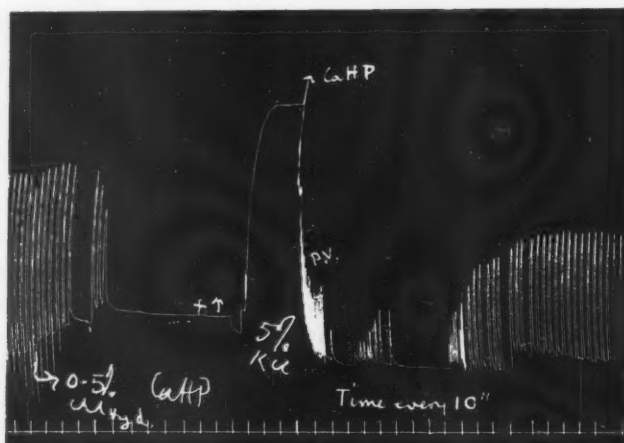
FIG. 1.   0·5 per cent. Chl. Hyd. CaHP = addition of 0·5 per cent. of chloral hydrate to a perfusing solution containing 0·6 per cent. NaCl, 0·03 per cent. KCl and saturated with the dibasic phosphate of calcium.   At the points marked with dots the heart was excited with strong single induced shocks.
Between + and ↑ the ventricle was faradized.
5 per cent. KCl = perfusion of 5 per cent. KCl in 0·6 per cent. NaCl.
↑ CaHP = solution mentioned above minus chloral hydrate perfused.
P. V. = the potassium chloride solution was pumped out of the heart and each pump stroke notches tracing.

Such and other facts led me also to suggest that two different structures might exist in muscle. The one structure, the excitable structure, capable of being excited by the ordinary induced shocks, and when so excited capable of exciting contraction in another muscular structure, the contractile structure.

Some time subsequently a somewhat similar series of experiments were published by Mines and Dale, who also found that the level of the contraction process in muscle was different from that of excitation. Apparently, however, they did not take precautions to ascertain if their analytical agencies induced contraction in the same material as did their electrical stimuli, and unless such

have been taken the possibility of the presence of more than one kind of contractile material is one that vitiates the conclusion.

A more general account concerning these muscular functions is given by me in a note published in the *Proceedings of the Physiological Society* (8). I have chiefly employed potassium salts as analytic agencies, and an example of their use is given in the accompanying diagram (see Fig. 1).

The tracing shows first the series of successively dwindling heart-beats which followed the addition of an excess of chloral hydrate to an otherwise adequate saline perfusing solution. The heart finally stopped visible activity in the dilated electrically inexcitable condition. When in that state a strong solution of potassium chloride was perfused through it, with the result that the heart now passed from the dilated to the contracted condition. Subsequently, on substituting an ordinary Ringer for the potassium solution, the heart relaxed and resumed spontaneous activity. A reasonable objection that may be raised against the experimental method lies in the strength of the potassium chloride solution which can conceivably seriously damage the heart. It will be admitted, however, that the tracing above gives no evidence of any such damage having been done, and, in passing, one other fact may be given on this point. The first illustration of the beats of a frog's heart taken after that heart had been perfused for twenty-four hours previously with an inorganic saline solution is given in a paper of mine published some time ago (2). That heart also had been treated with potassium, as was the one above. Previous observers have noted death of the heart perfused with saline solutions over such a length of time.

If there be borne in mind the mental picture of the series of gradually lessening beats given out by a heart when on the way to stopping in diastole, there will also be obtained a general picture of cardiac failure associated with preservation of the function of contraction as observed under experimental conditions. Special agencies are now required, however, to demonstrate the presence of contractility, because those who are normally and more commonly used are no longer adequate.

Substances do exist, of course, which are capable of destroying, or at any rate of permanently modifying, contractile material. But when they destroy it they usually evoke contraction in the process, and I have always used the term 'rigor contraction' to denote artificially evoked cardiac contractions accompanied by permanent modification of contractility. It must be regarded as universally true, however, that any such permanent modifications of contractile material are never the immediate cause of stoppage of the heart in diastole.

The possibility that there is more than one kind of contractile material in the heart is one that requires early consideration in dealing with the question of the cardiac reserve. It is one that has frequently been suggested, and as an example one may take the well-known theory of Botazzi (1) concerning the independent contractility of the sarcoplasm. And inasmuch as the cardiac reserve may conceivably lie in some special kind of contractile material only occasionally brought into play, e. g. the sarcoplasm, whereas the ordinary work
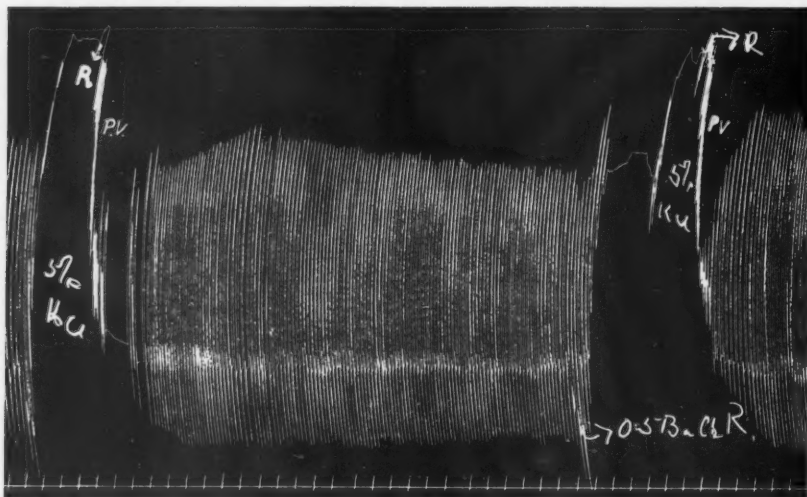
FIG. 2 A.

FIG. 2 B.

FIG. 2.   R = Ringer's solution of the composition 0·6 per cent. NaCl, 0·025 per cent.
CaCl$_2$, 0·03 per cent. KCl, 0·01 per cent. NaHCO$_3$.
0·5 BaCl$_2$R = the addition of 0·5 per cent. of barium chloride to the above.
5 per cent. KCl = perfusion of 5 per cent. potassium chloride in 0·6 per cent. NaCl.
P. V. = Forcible expulsion of a solution from the heart by manipulating the
rubber tubing connected with the cannula so as to imitate a pump.
The pressure variations so produced notch the tracing.
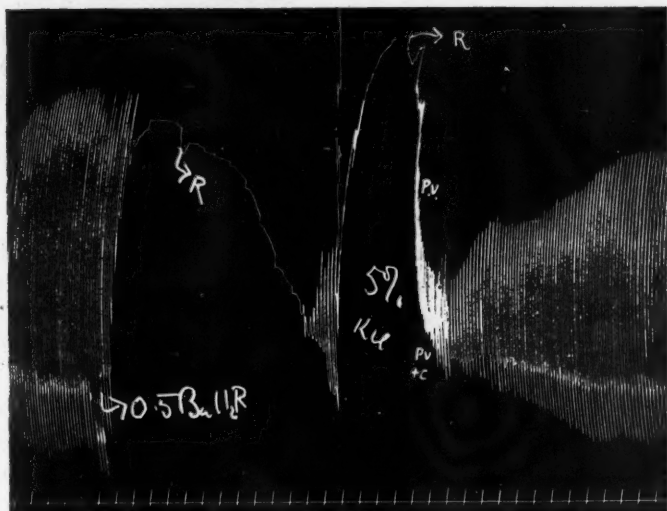
FIG. 2 C.

FIG. 2 D.

A period of nine hours had elapsed between the induction of the potassium contraction seen in Fig. 2 A and that seen in Fig. 2 D. For half an hour previous to taking Fig. 2 D the activity of the heart was as seen in the tracing prior to the induction of the potassium contraction. As ordinarily understood it was then moribund. But, as shown by these tracings, in spite of the great change that had taken place in the spontaneous activity, the amount of contractile material had undergone practically no change in the interval.

of the heart is done at the expense of anisotropic substance, such a theory is one that must either be incorporated into or rejected from the present argument.

Some time ago I utilized Botazzi's theory to explain the fact that potassium salts can evoke from the frog's heart two modes of contraction capable of super-position the one on the other and also evoked in definite order. The first contraction to appear—termed the 'tonic contraction'—was regarded as sarcoplasmic; and the second, the 'contraction effect', as due to anisotropic substance (2), (3), (7). The view does not now seem tenable.

If these two potassium contractions be evoked many times from the same heart, and we term x the amplitude of any 'tonic contraction' at the moment a 'contraction effect' was superposed upon it, and if we term the amplitude of that superposed contraction y, then we find a relationship of the form $x + y = C$, where C is some constant quantity (10). In practice x and y are simply the vertical distances through which the writing point of the recording lever moves on the usual smoked surface when these cardiac contractions take place, so that C is a measurement of height expressed in centimetres or any other convenient units. It is also possible for the amplitude of either of the modes of contraction in absence of the other to reach the value C. It may be mentioned that a sudden raising of the perfusion pressure determines the outset of the second mode of contraction (2) (7).

The only possible deduction from these results seems to be that the two contractions evoked by potassium take place at the expense of a single kind of contractile material, which, when exerting full activity, was capable of moving the writing point of my recording lever through a certain vertical distance, C. The fraction of this sum-total of contractile material utilized by the first mode of potassium contraction varied each time it was evoked. And according as this varied so did the second and superposed mode of contraction, for this second one then utilized the remaining portion of the contractile material, or what was left over, so to speak, from the first.

In every heart so far examined it has been found possible by the method mentioned above to determine the existence of a certain quantity, C. As determined it is a measurement of height expressed in centimetres, but it should rather be regarded as a number indicative of the sum-total of the contractile material of a heart. Its value varies from heart to heart, but it is a constant in any particular heart.

Its value can also be determined in other ways, and as a concrete example there is submitted with diagrams the superposition of a contraction induced by potassium on that induced by barium chloride several times in the same heart. (See Fig. 2.)

Barium chloride can induce reversible systolic arrest, but the amount of contraction induced by a particular dose may vary on each new occasion the contraction is induced. It varies in the diagrams above. So does then the amplitude of the potassium contraction superposed on it. But on each separate occasion the sum of the two contractions induced by these two substances was the same, as may be tested by actual measurement.

The spontaneous contractions of the heart are apparently capable of indefinite variation in amplitude between the limits zero and C, so that unless there are two forms of contractile material in the heart of equal contractile activity, on one of which the spontaneous contractions alone draw, and on the other all other modes of contraction, it seems probable that all modes of contraction use the same contractile material. An abundance of evidence in favour of this probability is given in other papers (2–7). It depends chiefly on the effects following the employment of substances capable of inducing rigor. The amount of rigor induced by such agencies is capable to some extent of being controlled. And when so kept within limits compatible with subsequent spontaneous activity of the heart it has been found that the amplitude of the contraction evoked by potassium is diminished. And according as the amplitude of the potassium contraction is diminished so is the amplitude of the
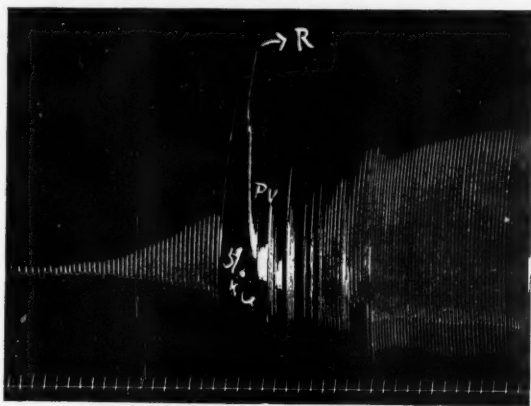
FIG. 3.   5 per cent. KCl = solution of 5 per cent. KCl in 0·6 per cent. NaCl.
R = perfusion of a solution containing 0·6 per cent. NaCl, 0·03 per cent. KCl, 0·025 per cent. CaCl₂.
P. V. = pressure variations induced as in Fig. 1.

spontaneous contractions permanently diminished. Indeed, it may be taken as a rule that the amplitude of the potassium contraction gives the maximum amplitude attainable by those of spontaneous origin. There is thus only one kind of contractile material in the heart, and by the method given above we are enabled to ascribe to it a certain quantitative value.

The majority of drugs do not alter the sum-total of the contractile material of the heart though they may greatly alter the amplitude of the spontaneous contractions. At any point of such variations, provided rigor-inducing substances have not been employed, it is possible to evoke by means of potassium salts a contraction of unchanged maximum amplitude. One example has already been given in the first figure. In that case the amplitude of the contractions had fallen to zero under the influence of chloral hydrate, but the heart contracted on application of potassium and relaxed on its removal. Another example is given in the accompanying diagram (see Fig. 3).

In the heart now considered there was present some process outwardly expressed by the gradually increasing amplitude of the spontaneous contractions. After a number of them had been recorded sufficient to indicate the trend of the process a potassium contraction was interpolated. It was of the same amplitude as that evoked previously by those salts from the same heart at a time when it was beating 'normally'. Whatever, then, may have been the cause of the original failure seen here on the part of this heart, it was not one which rendered contractile material unable to function. We are thus able by means of potassium salts to reveal in the background of these visible changes, as it were, a certain unchanged capital stock of contractile material. The amplitude of spontaneous contractions at any moment is the expression of the rate of interest on that capital at that moment.

It is also possible to 'exhaust' a heart, that is to say, to perfuse it with a particular salt solution until visible spontaneous activity finally ceases and the heart dilates and becomes electrically inexcitable, without there being any corresponding change in the amplitude of the contractions then to be obtained by means of potassium. Some form of rigor or coagulation seems a necessary preliminary to any diminution in the capital stock of contractile material. Other agencies seem to leave that capital unchanged despite the degree of alteration they may induce in its spontaneous manifestation of activity.

Bearing in mind the facts given above, and using the term 'cardiac failure' in the general sense of a diminished ability of the heart to beat spontaneously, it will be seen that there are observable in the frog's heart under experimental conditions two groups of phenomena to each of which the term cardiac failure may be applied. There are:

1. Cases in which the spontaneous contractions have decreased in amplitude but in which the amplitude of the contractions evoked by potassium remains unaltered;

2. Cases in which both the spontaneous contractions and the contractions evoked by potassium have decreased in amplitude.

Something has to be done to the heart, of course, to bring about these changes, even if that something only be the apparently negative act of perfusing the organ with Ringer's solution. But after that something has been done, whatever it may be, my experience has been that the heart may recover and beat well again only in cases of the first type; whereas in cases of the second type the heart is a permanently damaged machine. And inasmuch as in cases of the first type the heart preserves an unchanged store of contractile material which is able to contract, the failure that takes place is that of the ability of the heart to evoke the activity of its own store of contractile material, that is to say, the failure is a failure of excitation. And in cases of the second type the failure is to be regarded as a failure of contraction.

The next step to be taken is that of ascertaining if either of the two types of experimental cardiac failure described above has anything in common, or is comparable with that condition of the heart associated with clinical cardiac

failure. On this point the evidence is given by observations made on the action of drugs, of which attention may be chiefly directed to digitalis. This drug, and strophanthin, acts beneficially under experimental conditions in cases of cardiac failure associated with failure of the excitation process. Exhibition of the drug in these failing hearts was followed by an increase in the amplitude of the spontaneous contractions. But the increase lay within definite limits measured by the amplitude of the previously evoked potassium contraction. If the amplitude of the potassium contraction in these feebly beating hearts were a, and the amplitude of the spontaneous contractions were b, then, under the influence of digitalis, the amplitude of the spontaneous contractions could be increased from b to a, and no more. Pushing the digitalis further led to an increase of tonus and not to an increased amplitude of contraction. The same general principles apply to the other drugs and substances examined. They were found capable of exercising a beneficial action in experimental cardiac failure only in those cases in which that failure primarily resulted from changes in excitability. So far I have found no drug which enabled a heart to bring into play contractile material which did not react to potassium. *The spontaneous contractions may be less, but never greater in amplitude than the contraction contemporaneously evoked by potassium, and, according as they are less, so there is a contractile reserve which may be mobilized by drugs.*

The impression, given by these experiments, of the condition of the failing heart on which digitalis exerts a therapeutic action is that of one holding a certain stock of unused and temporarily unusable contractile material possibly because of some loss of excitability. It would thus seem reasonable that an investigation into the circumstances attending cardiac excitability would give information concerning the mechanism for maintaining and utilizing the cardiac reserve. The evidence indicates that mechanism to lie in a varying magnitude of the cardiac response to calcium.

The work was done on the hearts of known maximum contractility. It is obvious that without that knowledge the observer either does not know if the beating heart is maintaining a reserve of contractility, or, if he has a sort of belief there is such a reserve, he does not know its magnitude. But knowing the maximum, he knows the reserve at any moment as the difference between the spontaneous amplitude at that moment and the maximum. Moreover, he has a certain fixed magnitude with which the amplitude of the spontaneous contractions at any moment may be compared. At one moment that amplitude is 50 per cent. of the maximum; at another, it is 75 per cent., and so on.

A perfusing solution was then taken constant in composition except as regards its calcium content, and to this solution there was added sufficient calcium to evoke the activity of a definite proportion of the whole contractile material (12). The amount of calcium so required was altered by every substance I have examined capable of influencing the cardiac reserve. At least two factors are concerned which, under the conditions just mentioned, may be conveniently

E 2

expressed by equation of the type $\phi\,(x,\,y) = \dfrac{C}{2}$, where x is the tension of cal-
cium in the immediate neighbourhood of the excitable substance, y the state
of the heart at a time of trial, and C the maximum cardiac contractility.
Elsewhere I have suggested the factor y to be representative of the state of
aggregation of certain cardiac colloids (15), (5), (6).

Most drugs influence both the factors x and y in varying degrees.
y, however, cannot be properly appreciated by the more usual perfusing
methods. For example, its importance has hitherto been missed in experiments
with barium, although it is the finally predominant factor in the action of that
element. And it is then of such a character that drugs of the digitalis series
can act as antidotes to this action of barium. Attention is drawn to this point
here because attempts have been made to use barium salts clinically instead of
digitalis, a thing which would never have been done had the action of barium on
the factor y been properly appreciated, for it would then have been realized that
under the influence of barium the last state of the heart would be worse than
the first.

It seems also desirable to digress to meet the possible argument that
alterations in the relation of the heart to the other elements of Ringer's solution
have not been considered. That is not so, however, since I have shown else-
where that each of the other constituents of Ringer's solution, sodium potassium
and hydrogenion concentration, influences one or both of the two factors men-
tioned above and so is capable of expression in terms of calcium (2), (3), (4),
(5), (6). Moreover, when the ability of calcium to induce tonus or shorten the
refractory period is examined also, both these functional activities are increased
in magnitude similarly to that of the action of calcium in evoking spontaneous
contractions (5), (6), (13).

The majority of drugs which enable the heart to mobilize its contractile
reserve do so through the factor y. Their mode of action may then be
summarized in the statement that they increase the response of the heart to
calcium and thereby enable a given tension of that element to evoke the
activity of a greater proportion of the total contractile material than was the
case before the drugs were used (9), (11), (13). The state of affairs in cardiac
failure would thus appear to be that of an organ perfused with a solution
of too-low calcium tension to evoke the activity of an amount of contractile
material adequate to maintain a proper circulation.

Turning again to the experimental side, such a state of affairs may be
produced in two ways. We may either, maintaining a normal state of the
heart, reduce the tension of calcium in the perfusing solution below the
'adequate', or we may perfuse the heart with a solution containing what is
presumably a normally adequate tension of calcium and then alter the state
of the heart. In the first case we alter the factor x, in the second the factor y.
In both cases a drug which increases the response of the heart to calcium
enables it to maintain good activity. The result is attained in the one case

by rendering a normal heart sufficiently hypersensitive to calcium that it can work adequately on an abnormally low tension of calcium, and in the second case by bringing back to normal the response to calcium of a heart of reduced responsiveness thereto and so enabling it to work adequately on a normal tension of calcium. There is not enough evidence, however, to decide to which category the heart in clinical cardiac failure may be referred; whether it be perfused with blood of altered calcium tension, or whether it has a diminished response to calcium and unable to maintain adequate contractility on a normal calcium tension. By argument we directly assume an altered blood state of deficiency in the first case. We can account for the second also as the result of alterations in the blood. There may be circulating in the blood substances capable of rendering the heart desensitized to calcium. We need only consider a possible increase in its hydrogenion concentration.

In a paper published elsewhere I have shown that the heart may lose its normal power of combining with calcium if it be perfused with a solution of too-high hydrogenion concentration (4). This action is so marked that the heart then behaves in some respects almost as if it had been perfused by a fluid which precipitates calcium. We have evidence of an increased hydrogenion concentration of the blood in the respiratory distress associated with cardiac failure, but I do not know of any evidence showing that any such possible increase would depress normal cardiac activity, though experiments have been published giving the supposed limits of hydrogenion concentration compatible with the activity of the perfused heart. The last, however, are not altogether reliable guides. The limits, I find, alter with the composition of the perfusing solution, and although the limits given by any one observer may be quite correct for what he regards as the ideal Ringer's solution, they are not of universal application, as has sometimes been supposed. And so far as my own experiments go, the limits are much narrower for a fluid of the type I judge blood to be than for any of the recommended inorganic saline perfusing solutions. For the present, however, it is sufficient to note that the cardiac insufficiency in clinical cardiac failure can be regarded as one symptom associated with some form of blood change, though the possibility must not be excluded that the blood change itself may be secondary to some previous cardiac stress. During that period of stress waste products are accumulated which act adversely on the heart and reduce its activity below the point where there is balance between their production and elimination subsequently.

The waste products then increase further until the vicious circle thereby set up is broken by rest and digitalis. The mechanism of the maintenance and utilization of the cardiac contractile reserve thus appears to lie in the varying relations existing between the heart itself and the calcium of the perfusing solution, the blood. In ordinary circumstances the relation is such that the calcium does not evoke the activity of the whole of this contractile material. Sympathetic stimulation is the normal method of enabling the utilization of the whole of the contractile material, and, as I have shown elsewhere, during

the period of sympathetic stimulation a given tension of calcium can evoke the activity of a greater proportion of the total contractile material than was the case before (9) (11). There are in addition certain points connected with the maintenance of the 'ordinary' which, though outside the actual scope of this paper, seem, nevertheless, of sufficient interest to be treated here. These were elicited during experiments made to ascertain some of the differences between a heart containing blood and one perfused with any of the usual ignorance saline media. Their full description needs a paper in itself, and here we may be content with a short report on the results.

Briefly, it may be stated that the behaviour of a heart when the base of the ventricles is faradized is entirely different if the heart contain blood from what it is if the heart be perfused with any of the suggested modifications of Ringer's solution. In the former case effects are obtained in which inhibition predominates every time, in the latter only excitation is apparently present (14). The change takes place immediately Ringer's solution is substituted for blood. It is of the type always found in other circumstances when the balance of the inorganic constituents was altered so as to increase the tension of calcium. Keith Lucas by different methods has also demonstrated a greater tension of calcium in Ringer's solution than in blood (17). I found, however, that the tension of calcium in Ringer's solution could not be reduced to that of blood by reducing its calcium content, since when such was attempted certain phenomena were encountered which showed that the balance between sodium and calcium was disturbed in favour of the former (5). On the contrary, all the evidence pointed to the possibility that the inorganic saline solutions had a greater tension of calcium than blood because they had a much smaller tension of potassium. According as their potassium content was increased so they began to approximate to blood, but the approximation was not complete at a time when the amount of potassium added was such as rendered them unsuitable for maintaining cardiac activity. Traces of adrenin overcame their defects (12).

The possibility arising from these experiments is that blood regarded as a perfusing fluid contains a too great tension of potassium to be compatible with adequate cardiac activity except in presence of adrenin. We have evidence for this view in some of the symptoms of Addison's disease.

It is now generally admitted that the symptoms of this disease depends upon some loss of adrenin. But while agreeing that loss of the internal secretion of the suprarenal bodies may be a necessary antecedent to the appearance of the symptoms, we must at the same time realize that their *causa causans* lies in some defect of the bodily mechanism as it is without adrenin. We have a certain limited knowledge of the action of a perfusion fluid of too-high potassium content, and where we have that knowledge, viz. on the cardio-vascular and neuro-muscular systems, it corresponds to the symptoms of Addison's disease.

Summary and Conclusions.

1. The two muscular functions of contractile capacity and ability to contract in respect to excitation by induced shocks are entirely distinct. A muscle may have an intact store of contractile material able to contract, and yet, owing to loss of excitability, give no evidence of this on attempted excitation by induced shocks.

2. In every heart so far examined it has been found possible by appropriately employing potassium salts to demonstrate the presence of a certain capital stock of contractile material. For brevity this capital stock is designated C. C is a quantity varying from heart to heart but constant in value under ordinary conditions in any particular heart.

3. The variations in amplitude of the spontaneous contractions correspond to variations in the proportion of the total contractile material evoked by the normal stimulating agency of the blood. They lie apparently indefinitely between the limits zero and C. But at any point of these variations, unless some rigor-inducing agency has been employed, it is possible to show, by using the appropriate salt of potassium, that the heart maintains an unaltered capital stock of contractile material.

4. The majority of drugs, though they may cause very great variations in spontaneous activity, do not alter the value of C. Its value seems only altered by coagulation or rigor.

5. Two groups of phenomena are described in the frog's heart to each of which the term cardiac failure is applied. They are: (a) cases in which the amplitude of these spontaneous contractions has increased, but in which by using potassium it can be shown that the capital stock of contractile materials is undiminished—C unchanged; (b) cases in which the amplitude of the spontaneous contractions has diminished, accompanied by a corresponding diminution in the amplitude of the contraction then evoked by potassium—C diminished. The two types may be combined in any one heart.

6. Digitalis can restore the amplitude of the spontaneous contractions towards their original value in cases of the first type only. Accordingly it is concluded that the condition of the heart in clinical cardiac failure is of that type also.

7. An examination of cases of the first type shows that the failure in them results from alteration in the relation of the heart to the calcium in the solution perfusing it. Two subdivisions are found. There are: (a) cases in which the heart-beats are diminished in amplitude consequent on a decreased tension of calcium in the perfusing solution, the heart itself remaining 'normal'; (b) cases in which the composition of the perfusing fluid remains constant, but in which the heart itself reacts less vigorously to calcium than it did originally.

8. The mechanism for maintaining and utilizing the cardiac reserve is suggested to be as follows. The heart has a certain capital stock of contractile material, the activity of which is evoked by the calcium of the blood. Under ordinary circumstances the relations between the heart and the blood calcium are

such that the calcium evokes the activity of a certain proportion of the whole. By altering the magnitude of response of the heart to calcium a greater or less proportion of that whole is rendered active. During sympathetic stimulation a given tension of calcium can evoke the activity of a greater proportion of the whole cardiac contractile material than was the case before such stimulation.

9. In clinical cardiac failure the response of the heart to such amounts of calcium as are at present in blood is sufficient to maintain an adequate circulation. Digitalis is a drug which enables a given tension of calcium to evoke the activity of a greater proportion of the whole contractile material than is the case in its absence.

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A REVIEW OF SOME RECENT RESEARCHES DEALING WITH TYPHOID AND PARA-TYPHOID INFECTIONS

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IN this article some recent investigations connected with typhoid and para-typhoid infections are reviewed. They merit attention because of their practical applicability to clinical medicine and in that they provide improvements in clinical laboratory methods. The diagnosis of typhoid or para-typhoid infections rests on the recovery of the specific micro-organism from the blood, urine, or faeces, or on the demonstration of specific protective substances in the blood-serum. The recovery of the infecting bacillus is the most satisfactory method of diagnosis and it is fortunate that recent research has provided more efficient means to this end.

In the earliest stages of the disease cultivation of the blood is by far the most useful procedure. If the bacilli are present in the blood-stream in large numbers their recovery presents no great difficulty. The inoculation of 10 c.c. of blood into twenty times its volume of veal broth generally yields a positive result; or 8 c.c. may thus be dealt with, whilst 2 c.c. are incubated in sterile ox-bile. When few bacteria are present in the circulating blood, or when the latter is becoming loaded with newly-elaborated bactericidal substances the greatest care is necessary, and every device must be employed to protect the bacilli from harmful influences. Sir A. E. Wright has recently shown that bacteria may be classified as serophytes and sero-saprophytes. 'The serophytes would be those which, presumably because they find their food-stuffs ready made in the blood-fluids, are at home there. The sero-saprophytes would be those which cannot grow and multiply in the blood-fluids until a change has passed over those fluids, until the albuminous substances of the blood has undergone some sort of preparatory transformation.' He conceives this transformation as coming by a digestive process, and he has shown that not only is the blood-serum anti-fermentative or, as it is now usually styled, antitryptic, but that during bacterial infections this antitryptic power is considerably raised. It will be readily understood that rapid dilution of the bactericidal blood combined with neutralization of its antitryptic action by

the addition of trypsin will protect the bacilli and render possible their multiplication in a suitable medium. Further assistance may be obtained by introducing a quantum of dead bacilli into the medium with a view to absorbing the anti-bodies of the blood. The following experiment made at the Research Laboratory, No. 13 General Hospital, B. E. F., by Sir A. E. Wright, brings out the advantages to be obtained from such procedures :

| | Typhoid Emulsion Diluted. | | | | |
	10-fold.	100-fold.	1000-fold.	10,000-fold.	100,000-fold.
Serum A. B.* + Typhoid Emulsion	+	+	+	0	0
Serum A. B. + Typhoid Emulsion + Trypsin 1/30	+	+	+	+	+
Serum A.C.I.† + Typhoid Emulsion	0	0	0	0	0
Serum A. C. I. + Typhoid Emulsion + Trypsin 1/30	+	0	0	0	0
Serum A. C. I. + Dead Typhoid + Typhoid Emulsion	+	+	+	+	+
Broth + Typhoid Emulsion	+	+	+	+	+

* A not recently inoculated person.   † A recently inoculated person.

It is only in the early days of the disease, or before the development of protective substances, that blood culture yields positive results in a high percentage of cases. For this reason the blood should be cultivated as soon as the suspicion of enteric infection arises. The removal of 10 c.c. of blood from a vein by acupuncture is a simple, safe, and painless procedure, yet it is frequently neglected until too late.

When typhoid bacilli are excreted in the urine their recovery in pure culture from a catheter specimen presents little difficulty. Surface cultures on agar plates are all that is required.

In all but the earliest stages of the disease it is to examination of the faeces that we must turn for the recovery of the bacilli. Many conditions combine to make this examination difficult and uncertain. A host of bacteria inhabit the lower intestinal tract in man, many of which belong to a group of bacteria closely related in their morphological, tinctorial, and cultural characters to the typhoid–para-typhoid group. For many years efforts have been directed towards perfecting the technique for the recovery of typhoid bacilli from the faeces. Two recent researches promise to bear really practical fruit in this connexion. Dreyer, who for some time had been studying the biochemical action of actinic light, decided to investigate its effect on the bacteria of the colon and typhoid groups. His method consists in the subjection of an ordinary agar plate liberally spread with an emulsion of faeces to a graduated exposure of the rays of an arc light. The arc formed between water-cooled silver electrodes consists of a perfectly cold green light containing many of the ultra-violet rays of the spectroscope. Complete sterilization of the plate is obtainable by exposure of a certain duration. Shorter exposures kill off the less resistant bacteria whilst allowing the more resistant ones to survive.

In this way relatively large quantities of faeces may be rapidly ' diluted ' and individual colonies of typhoid or para-typhoid bacilli may be obtained within twelve to twenty-four hours. A selective action is not to be attributed to the rays, but to certain exposures typhoid bacilli are resistant and multiply freely.

Dreyer, Ainley Walker, and Gibson tested the method on mixtures of B. typhosus and B. coli and found that in every case where there were not more than fifty B. coli to each B. typhosus numerous isolated colonies of the latter were always found on some portion of the exposed area of the plate. Where there were more than fifty but less than 200 B. coli to each B. typhosus a few colonies at any rate of the latter were almost always discoverable.

The method has already yielded such satisfactory results when applied to examination of the faeces that the verdict of an extended trial is awaited with interest.

A further modification of technique suggested by the same authors is worthy of consideration. They investigated the suitability of various so-called selective media for the cultivation of the typhoid group of bacilli. Their results show quite conclusively that, far from being suitable culture media, the majority have a definite bactericidal effect on the bacteria. The following quantitative experiments will serve as examples :

1. *Showing the number of Colonies which grew on the various Media in Experiments made with various known Dilutions of Pure Cultures of B. Typhosus and B. Coli respectively*. (The experiments denoted by the same number were made at the same time in each case.)

Medium.	Number of colonies on plates inoculated with B. typhosus. 20 c. mm.			Number of colonies on plates inoculated with B. coli. 20 c. mm.		
	Experiments.			Experiments.		
	(1)	(2)	(3)	(1)	(2)	(3)
Ordinary agar . . .	265	150	90	1100	550	86
Endo's medium . . .	245	135	85	1000	500	60
MacConkey's medium . .	2	1	0	950	450	70
Drigalski-Conradi medium .	2	0	0	1050	500	64

2. *Showing the number of Colonies of B. Typhosus and B. Coli respectively which grew from Mixtures made at the same time from the same Cultures so as to contain* (a) 3 *B. Coli to each B. Typhosus, and* (b) 149 *B. Coli to each B. Typhosus.* (The mixtures were diluted 1/62500 before plating.)

Medium.	A 3 B. coli to each B. typhosus. 20 c. mm.		B 149 B. coli to each B. typhosus. 20 c. mm.	
	Typhoid colonies.	Coli colonies.	Typhoid colonies.	Coli colonies.
Ordinary agar	133	430	1	500
Endo's medium . . .	120	400	0	450
MacConkey's medium . .	1	460	0	420
Drigalski-Conradi medium .	0	303	0	400

3. *Showing the number of Colonies of B. Typhosus and B. Coli respectively which grew from Mixtures made at the same time from the same Cultures so as to contain* (c) 1 *B. Coli to each B. Typhosus, and* (d) 19 *B. Coli to each B. Typhosus.* (The mixtures were diluted 1/62500 before plating.)

Medium.	C 1 B. coli to each B. typhosus. 20 c. mm.		D 19 B. coli to each B. typhosus. 20 c. mm.	
	Typhoid colonies.	Coli colonies.	Typhoid colonies.	Coli colonies.
Ordinary agar	100	132	4	150
Endo's medium . . .	75	114	3	136
MacConkey's medium . .	1	121	0	161
Drigalski-Conradi medium .	2	75	0	152

Obviously agar is the best medium for the cultivation of the typhoid bacillus, and of the differentiating colour media Endo's fuchsin-agar is to be preferred. It may be stated in passing that considerable experience is required to pick out 'likely' colonies for further investigation. This is especially true for cultures on ordinary agar. In the light of these investigations Endo's medium assumes so important a position that the details of its preparation are given. They should be rigidly adhered to.

A litre of 3 per cent. agar prepared as usual, boiled, filtered and rendered neutral to litmus with 4 per cent. sodium hydrate. Add 10 c.c. of a 10 per cent. solution sodium hydrate, 10 gr. lactose, 5 c.c. filtered saturated alcoholic solution *basic* fuchsin. Mix. Add 25 c.c. of a *freshly* prepared 10 per cent. solution sodium sulphite. (When hot this is now fuchsin red.) Filter through cotton-wool which has been sterilized moist in the funnel for ten minutes in Koch's steamer. Distribute in 100 c.c. flasks with cotton plugs covered with brown paper. Sterilize five minutes at 115° C. in autoclave. *Store in the dark.* For use: melt in water at 100° C., and make plates in usual way twenty-four hours before required. Keep in the dark.

B. coli red with metallic sheen. The red diffuses into medium.

B. typhosus colourless.

Para-typhoids pink.

Browning, Gilmour, and Mackie recommend, in addition to direct plating, the use of a liquid medium consisting of peptone water containing brilliant green. They describe their medium as follows:

The fluid medium consists of 2 per cent. peptone and 0·5 per cent. sodium chloride in distilled water, steamed in a Koch's sterilizer (for three-quarters of an hour) and then filtered through ordinary filter paper. The reaction should be corrected if necessary till it is only very faintly alkaline to litmus paper. The medium is then sterilized by steaming or in the autoclave; when large numbers of specimens of faeces have to be examined simultaneously time is saved by sterilizing the medium in bulk, otherwise it should be distributed in amounts of 10 c.cm. in test-tubes and then sterilized. A stock 1 per cent. solution of brilliant green in distilled water is prepared; this keeps for many

weeks or even months.   Immediately before use a 1 in 10,000 dilution is freshly made up by adding 0·1 c.cm. of the stock solution to 9·9 c.cm. of distilled water and then this dilution is added to the peptone water.

They recommend that varying amounts of the dye should be added to the 10 c.cm. peptone water tubes, for each specimen of faeces a series of five concentrations being employed—namely 0·1, 0·2, 0·35, 0·5, 0·7 c.cm. of 1 in 10,000 brilliant green.   With a view to saving time and material, advantage may be taken of the experience of Clarke, Stokes, and Smith, who have recently tested the method on a large scale.   They find that a fluid medium containing 0·5 c.cm. of brilliant green 1 in 10,000 to 10 c.cm. of peptone water represents the average optimum quantity for the isolation of the specific micro-organisms.

They emulsify the faeces with several volumes of sterile water ; the mixture is then allowed to sediment (half an hour), and then five or six large loopfuls of the supernatant fluid, free from grosser particles, are added to the tubes of fluid medium.   When such a rich inoculation is employed, subcultures are best made after nine hours' incubation at 37° C.   When the specific organisms are found they usually occur in abundance in one or more of the subcultures.

Occasionally brilliant green resisting bacilli, mostly immune fermenting varieties of the B. coli group, abound in the faeces and outgrow the B. typhosus. The addition of telluric acid to the brilliant green medium overcomes this difficulty.   Browning and Thornton find that the addition of this chemical is not precisely of the nature of a summation.   It is therefore advisable to use a series of doses of brilliant green each along with 0·4 c.c. telluric acid 1 in 1,000 per 10 c.c. peptone water.   After incubation of the liquid media for 20–24 hours at 37° C. streak subcultures are made on plates which are then incubated at 37° C. for 18–24 hours.

Dreyer, Ainley Walker, and Gibson have shown that the effect of brilliant green on a mixture of B. coli and B. typhosus is to decrease relatively the number of B. coli while relatively and absolutely increasing the number of B. typhosus.   They recommend that subcultures from the liquid medium should be made on agar or Endo's fuchsin agar for the reasons stated above.   To summarize, the following technique for the recovery of typhoid or para-typhoid bacilli from the faeces is recommended : Examine the faeces as soon as possible after they are passed.   In the case of ' carriers ' administer a purgative, for the examination is made easier if the motions are semi-formed.   Emulsify a portion of the faeces in sterile broth, not in salt solution, which may damage a number of bacilli.   Centrifrugalize sufficiently to precipitate the coarser particles.

Inoculate agar plates with the supernatant fluid.   If Dreyer's arc light is available only one plate is needed and this may be heavily inoculated.   Failing this, proceed by the usual method of dilution.   Further, inoculate tubes of brilliant green peptone water, incubate and, as soon as sufficient growth has occurred, subculture on to Endo's medium.   Compared with the procedure of direct plating on to MacConkey's medium a considerably larger percentage of positive results are obtainable by the above methods.

The next stage is to deal with the isolated 'likely' or 'suspected' colonies. The procedure to be adopted may be conveniently exposed in tabular form.

```
                                  Lactose
                                     |
           ┌─────────────────────────┴─────────────────────────┐
   No production of acid and gas                      Production of acid and gas
 Typhoid, Para-typhoid, Dysentery,                              B. coli
           Gaertner
              |
           Mannite
              |
     ┌────────┴──────────────────────┬──────────────────────┐
 Production of acid and gas       No action          Production of acid
     Para-typhoid A            Dysentery Shiga           without gas
     Para-typhoid B            Morgan No. 1                Typhoid
       Gaertner                                      Dysentery Flexner
          |                         |                         |
   Neutral red broth            Motility                  Motility
          |                         |                         |
   ┌──────┼──────────┐        ┌─────┴──────┐          ┌───────┴────────┐
Cherry red  Canary  Red, green  Motile   Non-motile  Motile      Non-motile
  Para-     yellow  fluorescence Morgan    Shiga     Typhoid      Flexner
 typhoid A  Para-   Gaertner     No. 1
            typhoid B
```

Each micro-organism is then tested for its further confirmatory characters as set forth in the table below, and, most important of all, its agglutinability by a specific immune serum.

+ = Acid and gas. * = Acid, no gas. Litmus Milk {acid / alkali} formation. tion = +	Lactose.	Saccharose.	Dulcite.	Adonite.	Inulin.	Dextrose.	Mannite.	Sorbite.	Milk Clot.	Proskauer.	Indol.	Motility.	Liq. of Gelatine.	Litmus Milk 3 days. Acid forma-tion.	Alk. forma-tion.	Neutral Red Broth.
I B. faecalis alkaligenes	0	0	·	·	·	0	·	·	0	·	0	+	0	0	+	
B. Morgan No. 1	0	0	0	·	0	+	0	0	0	0	0	+	0	0	0	
B. dysenteriae 'Shiga'	0	0	0	0	0	*	0	0	0	0	0	0	0	0	+	
B. dysenteriae 'Flexner'	0 or *	0	0	0	0 or +	*	*	0	0	0	+	0	0	0	+	
II B. typhosus	0	0	0	0	0	*	*	*	0	0	0	+	0	+	0	Magenta, 24 hours
B. para-typhosus 'A'	0	0	+	0	0	+	+	+	0	0	0	+	0	+	0	Cherry red, 24 hours
B. para-typhosus 'B'	0	0	+	0	0	+	+	+	0	0	0	+	0	0	+	Canary yellow, 24 hours
B. Aertyck (enteritidis)	0	0	+ (0)	0 (+)	0	+	+	+	0	0	0 (+)	+	0	+	0	
B. Gaertner (enteritidis)	0	0	+	0	0	+	+	+	0	0	0	+	0	0	+	Red with green fluorescence, 24 hours

Henderson Smith has recently published a detailed account of the procedure adopted at the Lister Institute of Preventive Medicine. Those interested in the subject may further consult the *British Medical Journal* of July 3, 1915, or apply for reprints to Dr. Henderson Smith at the Lister Institute.

It will be noticed that the final verdict depends upon the positive agglutination test with specific immune sera. Great care is needed in the performance of

such tests, and practical experience emphasizes the importance of using broth cultures for the purpose. Colonies to be tested should be inoculated into 5 c.c. of veal broth and incubated for 16–20 hours at 37° C. Then 0·1 c.c. of 1 in 20 commercial formalin is added and the tube allowed to remain at room temperature for at least one hour. The agglutinability of the culture is then tested with standard agglutinating sera to which reference will be made below.

At this point we may conveniently break off and take notice of some recent improvements in the technique of the agglutination test and of some researches connected with the clinical value of this reaction.

Dreyer has drawn attention to a technique he devised some ten years ago and which places in the hands of the profession a method which gives universally comparable results. He prepares standard agglutinable cultures of B. typhosus, B. para-typhosus A and B. para-typhosus B by growing the bacilli in veal broth, subsequently killing them with weak formalin at 0° C.

Three agglutinable strains are kept as standard, and all subsequent cultures are quantitatively tested against these cultures. Thus each culture bears a figure which expresses its agglutinability compared with the standard. By this means the agglutinating power of any serum may be expressed in standard agglutinin units. Standard agglutination is the highest dilution in which marked agglutination (without sedimentation) can be detected by the naked eye. When the standard degree of agglutination occurs with standard agglutinable culture of a serum dilution of 1 in x, then x divided by the figure given on the label of the culture employed gives the number of standard agglutinin units contained in 1 c.c. of the serum examined. Dreyer suggests that for uniformity and simplicity in recording results they should be expressed in standard agglutinin units. The titre of agglutinating sera can be accurately determined by the use of standard agglutinable cultures, and each serum so tested becomes a standard agglutinating serum. Standard agglutinable cultures and standard agglutinating sera are obtainable from the Department of Pathology, University of Oxford, on behalf of the Medical Research Committee. The method has recently been tested on a larger scale by Dreyer, Ainley Walker, Gibson, and Inman, and its superiority over other methods is not to be denied.

It is to be hoped that full advantage will be taken of this enterprising venture, and that henceforth accurate quantitative tests will be recorded in place of the laconic statement, 'Widal positive'.

As regards the clinical value of the agglutination test certain questions have recently arisen seeing that epidemics of enteric disease have occurred among soldiers, the largest proportion of whom have been inoculated with a prophylactic dose of typhoid vaccine. Dreyer and Inman have investigated the agglutinin content of the blood in a number of normal inoculated persons, and find that for at least eight months after a single or double dose of typhoid vaccine the serum of all of them contains relatively large quantities of agglutinin. The maximum content of agglutinin per c.c. of serum found in any

inoculated person was 1,500 standard agglutinin units; and no inoculated person showed less than thirty units per c.c. of his serum.

On the other hand, it may be mentioned that in no case of thirty persons examined at different times and places has the serum of non-inoculated individuals, who had not had typhoid fever, ever exhibited an agglutinin content reaching ten units per c.c. of serum.

Persons who received two doses of vaccine usually, but not always, exhibited a higher agglutinin titre than those who had only one dose. Although the titre of the serum in persons who had not been inoculated before, and only received a single dose of vaccine, may in some instances at first be as high as or even higher than that of those who received two doses, it was found that after a certain lapse of time it falls to a lower level than in the latter individuals. In persons who had been inoculated before (within six years) the agglutinin titre maintained a high level for a longer period than in the case of those not previously inoculated. The importance of repeated inoculation is therefore clearly not so much that it induces of necessity a higher initial immunity, but that it ensures with certainty a more persistent one.

Seeing that the serum of inoculated subjects contains relatively large quantities of agglutinin for a considerable period of time, it remained to determine in how far this affected the agglutination test as an aid to diagnosis. Dreyer, Ainley Walker, Gibson, and Inman have investigated the matter and find that the presence in the serum of agglutinins resulting from inoculation of a typhoid vaccine in no way diminishes the diagnostic value of the reaction. An accurate differential diagnosis can be made by testing the patient's serum at repeated intervals against B. typhosus, B. para-typhosus A and B in a parallel series of observations, the maximum dilution of the serum in which agglutination takes being always determined.

If the individual is suffering from active typhoid infection his titre of typhoid agglutination will exhibit the usual rise and subsequent regular fall seen in non-inoculated subjects, but starting from and returning towards the higher base-line of inoculated persons.

If the individual is suffering from active para-typhoid infection one of three things may occur as regards his typhoid agglutination titre, namely, (1) no appreciable change may occur in the titre ; (2) a relatively slight rise may occur, followed by a fall towards the former level; (3) a marked rise may occur synchronous with the rise in para-typhoid agglutination titre and subsequently followed by the usual fall towards the former level. Meanwhile the titre of para-typhoid agglutination runs the normal course of rapid rise to a maximum (usually exceeding the maximum typhoid titre) followed by a fall, which slowly reaches a point *below* the persistent base-line of typhoid agglutination of inoculated persons. In the case of mixed infections, whether in inoculated or non-inoculated persons, the agglutinin curves for the different infecting organisms are usually not synchronous, and they pursue their ordinary course independently of each other.

For routine purposes the blood should be tested on the twelfth, sixteenth, and twentieth day of disease in early cases, or on the twenty-fifth, thirtieth, and thirty-fifth day of disease in late cases. Such a series of examinations involves a certain amount of time and labour, but the information gained is so trustworthy and has such practical value that its general adoption as a routine clinical method is confidently recommended.

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MULTIPLE TELANGIECTASES WITH EPISTAXIS OF THE FAMILIAL TYPE

By ROBERT HUTCHISON AND W. JENKINS OLIVER

With Plate 5

In this series of three cases two of the patients showed multiple telangiectases of the face with lesions on the buccal mucous membrane; all three gave a story of frequent attacks of epistaxis occurring since their early years, with a definite history of nose-bleeding in other members of the family.

Case I. John G., a carman, aged 49, widower, was admitted to the London Hospital on August 4, 1915. He gave the following history: All his life for as long as he could remember he had had attacks of epistaxis, which had been more severe during the last two years, especially in the morning. The bleeding persisted even when he was in bed and often occurred after meals. Spontaneous bleeding from the lips, sometimes preceded by a feeling of soreness, began about eight years ago, but these had until his admission entirely ceased during the last two years. He had bled occasionally from the ears about the fossa of the helix and from the corner of the right eye, also from the gums and from the inside of the mouth, especially after very hot drinks. He had noticed some bleeding from the rectum on straining about one year ago. From the dilated superficial vessels on the nose occasional bleeding had spontaneously occurred during the last six years, and he was for this reason unable or afraid to wash in warm water. He had never observed any haematuria, haemoptysis, or haematemesis of fresh blood, but had frequently vomited swallowed clotted blood. The red spots and vessels had been first noticed about eight years ago and were increasing in number. According to his own account he had always been in the habit of passing a rather large quantity of urine, and had for years had to get up some two or three times during the night to micturate. For the last three years he had suffered from swelling of the feet and legs to above the knee on long standing or on doing any heavy work. This was associated with some shortness of breath; the swelling always disappeared when he was in bed. He suffered frequently from headaches and used to experience giddiness on stooping. There was no cough, vomiting, or tinnitus. He had a good appetite with no flushing after meals, no diarrhoea, and the bowels were regular with medicine. He had had rheumatic fever at the age of fifteen years. In 1912 he was admitted to an infirmary complaining of epigastric pain and epistaxis, when his condition was diagnosed as pernicious anaemia. He had remained in that institution for two and a half years, being discharged in May, 1915, since which date he had been losing weight. Until his admission to the infirmary in 1912 he had been accustomed to take six to seven half-pints of ale per diem, with rum occasionally; he considered himself to be a heavy smoker. He denied having ever had any venereal disease. He did not bleed particularly readily if he cut himself, and the bleeding from the dilated vessels on the lips and nose was quite easily stopped by the application of cold water. The bleeding was, as a rule, rather more frequent during the summer months. He had no chilblains during the winter,

but at this time the numbness and cramp in the toes, which he always experienced each morning, and occasionally in the finger-tips, was more intense.

Skin condition. On the nose, symmetrical malar parts of the cheeks, and on both auricles were numerous punctate red spots and dilated vessels, the inner cranial surface of the left auricle showing larger punctate lesions than the right. The pattern of the telangiectatic vessels was irregular with no formation of definite spider naevi. Both lips showed large pin-head sized raised prominent red spots, and these were larger and more numerous on the lower lip, which was slightly everted. On the buccal mucous membrane—on the left more than on the right side—were numerous miliary red dots, which were seen also on the hard palate and about the tip and under surface of the tongue, at the sides of which appeared large vessels. On the posterior wall of the pharynx were some punctate red lesions. The soft palate and uvula were clear. From the punctate lesions on the lips dilated vessels passed inwards towards the gums. The trunk and limbs showed no telangiectases. The palms of the hands were dry, with the natural furrows very distinct. There was some slight thickening beneath the finger nails. Through some of these—on the right thumb and fingers 2, 3, and 4, and left fingers 1 and 2—were seen small round dots which did not alter definitely under pressure. About the dorsal surface of the right hand were some small bright-red round discrete lesions which disappeared on pressure. The largest of these towards the radial side of the metacarpal region of the thumb was raised above the surface, of the size of a hemp-seed; a smaller one was situated on the wrist towards the radial side, with two still smaller lesions on the ulnar side of the distal phalanx of the little finger. The legs showed no oedema, with no marked varicose veins. The skin was dry with a tendency towards scaling.

No retinal haemorrhages were observed, nor were the vessels recognized as being markedly dilated. It was reported from the aural department that the larynx showed nothing remarkable. *Ears.* On the left drum, behind the handle of the malleus, was a small reddish area suggesting a congested vessel. *Nose.* The nasal septum on both sides showed several punctate lesions, none of which was so prominent as those on the lips.

The patient was a thin man, rather deeply pigmented, anaemic looking, with no appearance of jaundice. There was considerable watering of both eyes. The tongue was furred and dry ; the teeth were carious and discoloured, with some pyorrhoea. There was no visible pulsation about the chest. The apex beat was in the fifth interspace in the nipple line. A systolic murmur following the first sound was audible at all the cardiac areas. A diastolic murmur could occasionally be heard to follow the second sound at the apex. Pulse 72, regular, of medium volume, tension not appreciably raised. The liver and spleen were not palpable. There was some redundant tissue about the anal orifice suggesting external haemorrhoids. Blood pressure (radial) = 110 mm. Hg (Riva Rocci). *Urine.* Average amount in twenty-four hours measured 70 oz. Acid—amber coloured— specific gravity 1,012—contained no albumin and no sugar. The temperature showed a daily excursion from morning 98–97·2° to evening 98·4–99·5° F.

The blood examination revealed secondary anaemia. The total number of red cells was 3,250,000 and of white cells 4,200 per c.mm. Haemoglobin 15 per cent. Colour index 0·2. A differential leucocytic count showed : Finely granular oxyphils 70·5, coarsely granular oxyphils 3·5, small lymphocytes 13, large lymphocytes 4·5, large hyaline 7·5, coarsely granular basophil 1 per cent. The blood coagulation time was 3 minutes 30 seconds.

The Wassermann reaction was negative. [NOTE.—The patient had received five intravenous injections of neosalvarsan during the last fifteen months of his stay in the infirmary.]

The lesions inside the nose were cauterized without checking the epistaxis or causing much general improvement. Calcium lactate gr. xv was given thrice

daily for a period of three successive days with a similar result. Under a general anaesthetic the lesions on the lips, and later those inside the nose, were treated with diathermy. Great improvement followed, so that the patient was discharged from hospital on October 9, 1915. He was then very cheerful and declared himself to be feeling better than he had done for many months.

Case II. Henry G., aged 77, the father of the above patient, came to the hospital together with the third patient by request for examination on Sept. 23, 1915. Since childhood he had had frequent spontaneous attacks of bleeding from the nose, with some bleeding from the gums during the last five or six months. Some two or three years ago there had been occasional bleeding from the rectum, with never any haematuria. He had had 'spots' on the face for years and he was unable to say when these had first appeared. There had never occurred any spontaneous bleeding from these lesions and he was not accustomed to bleed at all markedly from any wounds of the skin. He had a good appetite,
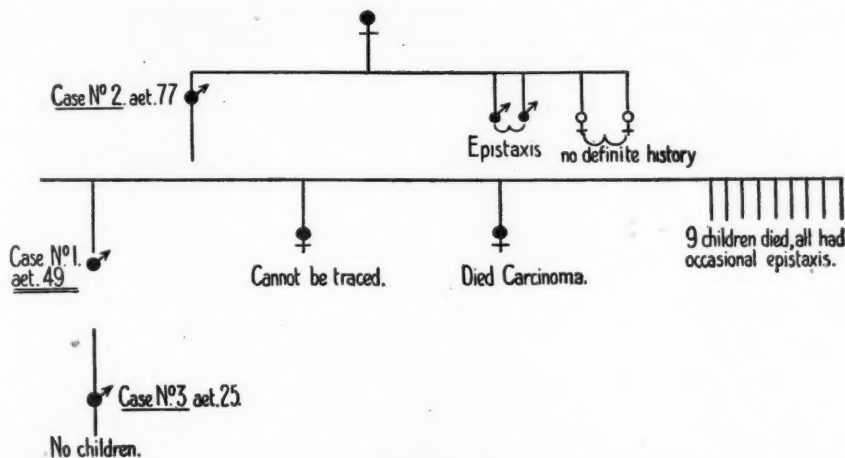
there was no flushing after meals, and there was a regular action of the bowels. He had usually a cough during the winter, but did not complain of any shortness of breath or swelling of the lower limbs. There was no headache or tinnitus, and he did not pass any specially excessive amount of urine, nor did he complain of nocturnal frequency. He had had pleurisy on the right side two years ago. He denied any venereal disease and there was no family history of tuberculosis. He had been a total abstainer for thirty-nine years and had not smoked for thirty-six years. From this patient's account and from that of Case I, the accompanying diagram of this familial affection was drawn.

Skin condition. Telangiectases were present on both auricles, the malar areas of the cheeks, and on the sides of the nose. Some of these had the appearance of spider naevi formation. There were no definite punctate lesions on the face. On the lower, with a smaller number of similar lesions on the upper lip, were small pin-head sized and miliary punctate spots which were not raised above the surface. On the dorsum of the tongue, especially about the tip, were numerous similar lesions, also on the hard palate, with a few scattered miliary dots on the buccal mucous membrane. The vessels on the uvula and soft palate were well defined. In addition to a few seborrhoeic warts on the back and shoulders were some bright red spots which faded under pressure. The subcutaneous veins were not very marked except on the inner surface of the left

thigh, and were rather obvious about the lower border of the costal margin. No varicose veins or external haemorrhoids were seen. The skin over the dorsal surface of both hands was thin and atrophic in appearance.

The patient showed a somewhat anaemic appearance of the face with much puffiness of the lower eyelids and considerable watering of both eyes. No unusual physical signs were observed in the chest or abdomen. Pulse 72, regular, with no large excursion, and rather high tension. The teeth were few and discoloured, tongue furred. There was some apparently chronic articular trouble of the right knee. Blood pressure (radial) = 155 mm. Hg. The urine obtained during this examination had a specific gravity 1,008, and contained no albumin and no sugar.

Case III. John G., aged 25, window cleaner, the son of patient Case I. He was married and had no children. For as long as he could remember he had been troubled with epistaxis, the attacks of which had not been so frequent during the last two years. There had been no bleeding from any other areas. No melaena. No haematuria. There was no flushing after meals and the action of the bowels was regular. He gave no history of chilblains or of any illness. He denied any venereal disease. He drank no spirits and only occasionally a glass of beer, but ' a lot of tea '.

Skin condition. No telangiectases on the face. On the right cheek were two raised reddish pink lesions with a similar larger one of nearly the size of a split pea just beneath the right eye. On the tip of the tongue and on the mucous membrane of the lips were some miliary red spots. The vessels on the uvula and soft palate were very well marked. About the right shoulder were a few raised discrete lesions, which disappeared under pressure but were not quite so pink as those on the face. The hands were cold and rather clammy, with a slight dusky appearance suggesting some circulatory stasis.

There was nothing remarkable in his general appearance, nor were there any physical signs of note. Pulse 54, regular, volume small. Blood pressure (radial) = 130 mm. Hg. Urine—specific gravity 1,008, contained no albumin and no sugar.

These three cases, then, form a definite series in this remarkable familial affection. Presumably the skin lesions and those of the nasal and buccal mucous membranes are naevoid in character and of the nature of angiomata. There did not appear to be any underlying pathological cause for the dilatation of the superficial blood-vessels of these regions. Although the second case showed a somewhat high blood pressure no definite signs of an associated interstitial nephritis were recognized. The low blood pressure in the case of the first patient may be attributed to the anaemia, and the more aggravated form of his epistaxis and his numerous skin lesions to the presence of the mitral incompetence, though this condition appeared to be fully compensated during the period when he was under observation. In none of the cases could any history of the indigestion which usually accompanies acne rosacea be obtained, nor was there any sign of any local atrophy in the neighbourhood of the skin lesions.

This disease was first described by Osler (1) in 1901, and since Parkes Weber's (2) contribution with many references in 1907 a few other cases have been described.

Osler's (3) last reported case had epistaxis which had begun at the age of 10 years, also bleeding from spots on the skin of the face, hand, arm, and frequently from the buccal mucous membranes. The blood coagulation time was

six to seven minutes, which became lowered by one and a half minutes with calcium lactate. The patient's grandfather, father, and one sister had had spots; the son, aged 20 years, had no spots but bled from the nose. Colcott Fox's (4) patient had epistaxis which had begun at the age of 10 years; the red spots appeared at 14, chiefly on the trunk. Considerable bleeding occurred from the rectum; rather slow pulse, blueness of hands. Coagulation time was 3 minutes 50 seconds. Here there was no definite family history.

Sequeira's (5) case was a woman, aged 55, in whom similar lesions had appeared during the six years previous to the time when she came under observation for bleeding from the left index-finger which she could not control. She had suffered for many years with morning attacks of epistaxis. The blood showed some slight secondary anaemia with a normal coagulation time. Her general condition suggested chronic interstitial nephritis. There was no family history of any similar affection, though one daughter had occasional attacks of epistaxis.

In publishing the notes of these three patients our best thanks are due to Dr. Lack and Dr. Patterson for their report from the aural department and for the treatment carried out by them, and to Dr. Panton for the blood examination.

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DESCRIPTION OF PLATE.

PLATE 5.   Photograph of Case I, showing spots on lower lip
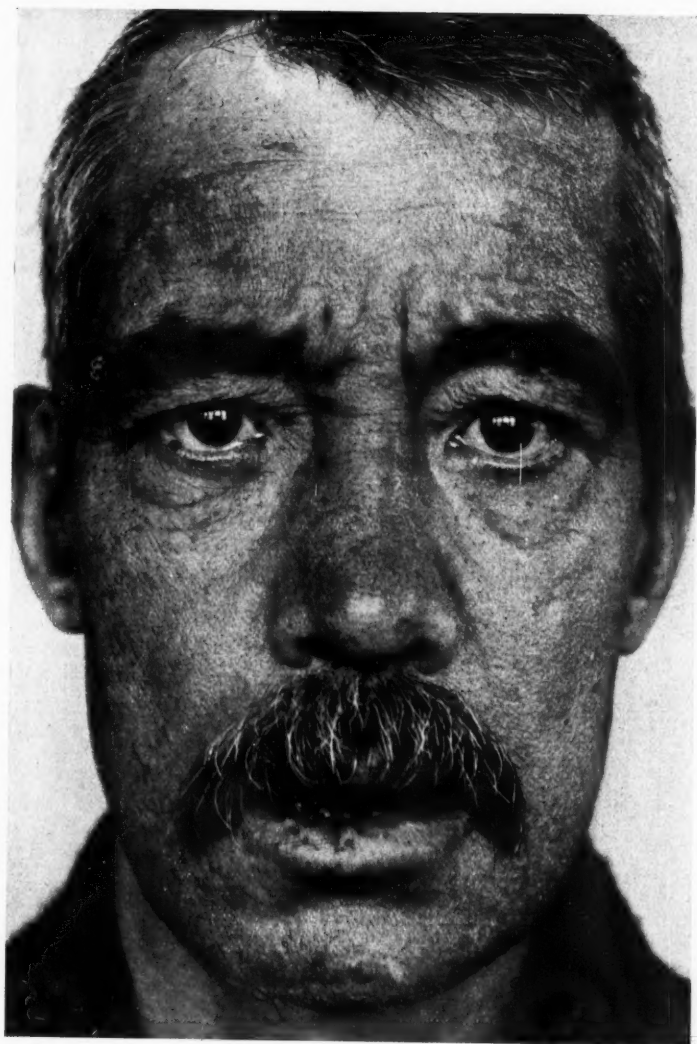
SOME FUNCTIONAL NERVOUS AFFECTIONS PRODUCED BY THE WAR

By F. E. BATTEN

THE clinical pictures presented by functional disturbance of the nervous system produced by the war are so varied, and give rise to manifestations so different, that it is difficult to co-ordinate the cases which come under this heading.

The time will come when it will be possible to consider separately the cases of mutism, amaurosis, loss of memory, the hysterical paralytic manifestations, the phobias, the psychoses, epilepses, and many other groups; but I am assured it will serve a useful purpose to review some of the various neuroses which have come under my own observation.

Group I. Cases with defined Paralytic Manifestations, Hemiplegia, Paraplegia of an Hysterical Nature.

It is interesting in this group to notice the different mental attitudes. The patient may be bright and smiling, and making every endeavour to perform the movement required, and in doing so puts the antagonistic muscles into the most forcible action. Such a patient is always a little better, but never is well.

In other cases the patient is morose and sulky, makes no attempt to perform the movement required, and will not respond to any suggestion. The result is the same in both groups because the patient is dominated by the dread of returning to conditions which have produced or to which he attributes the production of his symptoms.

Case I. A. van D. S., aged 22 years. A Belgian and in civilian life a baker.
On August 19, 1914, he was struck heavily in the abdomen with the butt of a rifle at Aerschot. He bled from the nose and mouth and lost power in both his legs. He was removed to Antwerp, where he remained till October 10; then he was transferred to the 1st General Hospital and remained there till November 14, 1914, when he was transferred to the National Hospital, Queen Square. At this time he walked on crutches.

He was a slightly built man, but otherwise well developed and nourished. He was a bright, lively, highly strung, emotional individual. He spoke Flemish, French, and German, and the latter language was used mostly in communicating with him; but he rapidly acquired sufficient knowledge of English to understand questions and commands.

When first admitted and asked to walk, the patient grasped the top of the crutches and pulled the body up by the strength of his arms; he then placed

each crutch alternately forward, allowing the whole weight to fall on the advanced crutch, and would advance the legs synchronously with the crutch. Later, when taught to walk in the walking machine, he would support the weight of the body on the hands, dragging the hindmost leg forward against a resistance produced by placing all the antagonistic muscles into forcible contractions.

At a later period he walked without the machine, but with the hinder leg as it were glued to the ground, from which it could only be moved by the most violent tugging efforts.

The same over-inaction of antagonistic muscles was present when asked to perform movements in bed, and yet in passive movements the legs were quite free.

Physical examination was entirely negative, all the reflexes were normal. There were certain skin areas which exhibited some hyperaesthesia. I had the advantage, at that time, of the help of Dr. Sweasey Powers acting as my clinical clerk, and he undertook the re-education of movements. At first there was considerable improvement, the crutches were abandoned, then the walking machine ; the patient was always bright and cheerful and pleased with his progress, but he never improved beyond the stage above described.

Other methods of suggestion treatment were tried—strong faradic applications to the back, complete rest in bed, isolation from the sympathy of his countrymen and the various visitors to the ward, who were charmed with his cheerful nature under such an affliction.

He was then sent to a private home for Belgian soldiers, in the hope that change of surroundings might help matters. He remained for four months under my care in the hospital and for six months under my observation, but it must be confessed that I entirely failed to cure him ; and yet, when first seen in November, 1914, I felt certain that he would rapidly recover. Recent report, November, 1915, says he is better but not fit to return to work.

About the same time a Welshman was under my care with complete paraplegia of six years' duration, from an injury to his back, who in three weeks was completely cured by the same lines of treatment.

I was perfectly confident that I could cure him, and told him so. I was equally confident in the case of the Belgian, but my means of expressing my confidence were limited by the difficulty of intercommunication imposed by language. Was this the cause of failure? It may have been a factor, but I think not.

The Welshman had made the journey to London under most difficult conditions and against the advice of his medical man. He had the wish to move his limbs and return to work, but could not.

The Belgian had passed through the horrors of war to a haven of rest and he had no wish to return to the former.

When war is over, he will, either with or without a journey to Lourdes, return in good health to his former peaceful avocation of a baker.

Case II. W. C., aged 21 years. Corporal in the Belgian army.
Was mobilized at the outbreak of war and fought continuously till October 27, 1914. He was in action on the retreat from Liège, at Termonde, Namur, Louvain, and Malines, and then at the siege of Antwerp.
After this he went into action again on the Yser, at Dixmude.
On October 27, 1914, he was knocked out by the explosion of several large shells. He was rendered unconscious, and remained so for some hours ; when he recovered he was in hospital at Calais.

When he came to he was able to see and hear perfectly well, but he was quite dazed and remembered nothing of his circumstances.

For a week he did not understand what was said to him, nor did he recollect the details of the accident; then his memory and full intelligence returned, except for periodical attacks in which he again became quite dazed. Since the onset he had been quite unable to move his legs.

His arms were at first weak, especially after a series of attacks he had in November and December, 1914, in which he struggled violently and had to be held down by several nurses. He called these fainting attacks, and said he did not move his legs in these, but only his arms. He said he could not move his head at all, nor his body or legs, but only his arms. He said, 'Sometimes I try hard and set my teeth, but I do not know how to move my head and my legs; I try, but they do not move.' There was no defect of the sphincter. He could see well, but if he attempted to read everything went black.

When admitted to the National Hospital on July 8, 1915, he was a thin, emaciated youth of normal intelligence. He was firmly convinced that he was seriously paralysed, and he had made most heroic efforts to help himself, without avail.

The musculature was very wasted generally, but there was no localized wasting beyond this. The patient said he could not lift his head, and if his body were lifted up his head at once fell back, or rather was definitely thrown back, and lolled about in a most alarming fashion. Yet as he lay in bed, he frequently lifted the head unconsciously and placed his hands under it. Also, when asked directly to lift his head, the sternomastoids went into strong contraction, but so also did the neck extensors, and the head became rigidly held with great strength in an extended position.

The patient expressed himself as completely helpless to move the trunk muscles, but could turn over readily in bed, and when trying to move his head the whole trunk was fixed in strong opisthotonos and the muscle power was seen to be normal. The abdominal walls were rigid. The upper limbs were generally wasted and there was some lack of effort in movement to order. But all movements were performed. The lower limbs lay extended and adducted and were generally wasted. When asked to move the limbs there was no movement whatever, but in various head movements the legs were observed to be strongly fixed in extension. There was no increase of tone, and in passive movement there was no active muscular resistance. There was indefinite blunting to all form of sensation. All reflexes were normal. He lay in bed unable to move.

Major Walshe, to whom I am indebted for the above notes, worked hard at this patient, inducing him firstly to lift his head off the pillow and then to move his legs. By the end of July, 1915, he could just sit up; by the end of August he could stand in the walking machine.

By the end of September he could walk with crutches, and by the end of October he could walk with two sticks, feet wide apart and moved as if glued to the floor.

He was always bright and cheerful, seemingly delighted with his progress, which he was always ready to demonstrate, but with a persistent amount of disability out of all keeping with his muscular powers.

He will eventually get well, but not, I think, before the end of the war.

Hysterical Monoplegia.

Case III. F. M., aged 21 years. A Belgian. Admitted April 8, 1915.

The patient, while riding a horse in Liège on August 8, 1914, was thrown, and the animal fell upon him. His friends freed him from the animal, but he

could not help himself. He did not lose consciousness. He could move and use his arm, but he could not use or move his left leg. He had no pain. He was carried to hospital. The skin was not broken, but he had a feeling of soreness in the lumbar region. The doctor diagnosed an internal injury. He was taken to the hospital in Brussels. For about seven days after the accident he had retention of urine, and was catheterized, and there was blood in the urine. Since then he had urinated normally. He was not sensible of his right leg. There was no feeling in it as high as Poupart's ligament, and he could not move it.

After spending eleven days in the hospital at Brussels he was removed to a hospital in Alost, near Ghent; while there the town was captured by the Germans. In November, 1914, he escaped to England, and with the aid of two comrades, one on either side, and a walking-stick, he was able to make his way to the coast and thence to Folkestone. He was sent from there to a hospital at West Malling in Kent, from whence he was sent to the National Hospital. While at West Malling he was treated with massage. The left leg increased in size, and for about one month he was able just to move the toes of his left foot, and had regained sensation in the bones of the left leg. He had not regained sensation of perception of touch or temperature in the same.

He was a powerfully built youth of 21 years. Skin and mucosae of good colour. Thoracic and abdominal viscera healthy. He was intelligent, and showed no noteworthy emotional abnormality; the speech was normal. There was no affection of special senses or cranial nerves. Head and neck movements were normal in range and power. Dorsal and abdominal muscles acted well, and the patient could sit up in bed without hands. Upper limbs were normal in power, tone, co-ordination, and nutrition. No tremor, no ataxy.

Lower limbs lay extended and adducted. The right was normal. The left showed a complete hysterical paralysis. There was probably an element of actual malingering in the picture. There was some general wasting of the limb, no local wasting of particular muscles. Thigh, 4 inches above patella—circumference on right $16\frac{1}{4}$ inches, left $14\frac{3}{4}$ inches. Calf, 5 inches below patella—circumference on right $13\frac{1}{4}$ inches, left $12\frac{1}{2}$ inches.

The patient did not move the limb at all when asked to do so, and there was no sign of effort on his part; though a few moments earlier, when he was undressing for examination, he was seen to lift the left leg as he sat on a chair well up into the air to pull off his sock. If the leg were lifted passively, and suddenly let go, it would subside gently on to the bed in a manner showing plainly that there was considerable power in the limb. There was very little associated movement of the affected leg in forced movements of the right leg, and this seemed due to careful inhibition of this natural association of movement of the two legs.

Sensory System. Below a level which varied from moment to moment, there was absolute loss of sensibility to touch, pain (cutaneous and deep), temperature, position and passive movement, but no loss to vibration. The disturbance was clearly purely functional. The perineum, scrotum, and penis possessed normal sensibility.

All the deep and superficial reflexes were normal. The plantar on the right was flexor. No trace of response obtained on left.

Gait. Walked with crutch with left leg held straight and off ground. It was held stiff in a manner unmistakably denoting active and voluntary power.

The patient was a sullen individual, quite unresponsive to any suggestion. Various methods were adopted showing that the power of the left leg was quite good, but he always relapsed into the condition of being unable to move the leg when in bed. As suggested by Sir William Gowers, ether was administered in

the hope of inducing an excitement stage, but unfortunately he took it quite quietly, and no such stage was produced. Whilst recovering the leg was put into a flexed position, and he maintained it in that position for some time, but the suggestion that he could move it failed, and as he fully recovered consciousness the limb resumed its former disability.

Isolation was tried, but without success. He was an irritable, sulky individual, who would make no effort, and he left the hospital in the same condition in which he was admitted.

Group II. Mutism.

The three cases of mutism which have come under my observation have all been due to, or attributed to, shell concussion, and have all rapidly recovered either spontaneously or with the most simple suggestion.

They have all been able to write an account not only of the shock but of their life in the trenches, and have been able to answer questions in writing. One such account is given in full as indicating how perfect the memory is for recent events. It has not been possible to verify the statements made, but there seems no reason to doubt their accuracy.

Case I. E. L., aged 26 years, went out to France on September 2, 1914, and was in the firing line from that time till May 8, 1915. He was quite well the whole time, and got a D.C.M.

On May 8, 1915, a shell burst over him, killing five and wounding three of his fellows. From that moment he lost his speech. He had a little pain in the head. He answered all questions in writing. The account which he gave of himself between May 8 and May 15, when he was admitted to the National Hospital, did not tally with known facts.

His account was that after the concussion he was not unconscious but could not speak; he was taken to hospital, remained there for one day, and then was transferred to England.

It was known by his medical case paper that he was taken to Rouen, and that he was there for three to four days; but he had no knowledge that he was there, though he was quite willing to admit that his papers proved it. There was a blank of four to five days for which he could not account, but he was quite certain that he was never unconscious.

On admission to the National Hospital on May 15 he was completely dumb. He understood all that was said to him, and he could write an account of himself and answer questions in writing. On May 17 he suddenly regained his speech, and by the 19th it was quite normal.

This patient was a most cheery individual, well made, and in excellent physical condition. He was a keen soldier and expressed himself anxious to return to the front.

To designate this case 'hysterical mutism' would seem to me a misuse of the term hysteria, and yet it is most difficult to draw the distinction between this and a true hysterical mutism. It would appear that a physical shock as well as a psychical shock can produce a mutism. The psychical shock is more likely to act on the unbalanced nervous system of an hysterical individual, whilst the

physical shock may affect the nervous system of the individual with the most perfect nervous balance.

Case II.   R. M., aged 30 years.   Whilst shoeing a horse on August 9, 1915, a shell burst overhead, knocking down both horse and man and rendering the patient unconscious.   He did not know how long he remained so, but when he came to himself he was in a clearing station.   Since then he had not uttered a sound or spoken a word.   In all other respects he felt well and complained of no symptom whatever.   He was quite cheerful in a quiet way.   He was a well-nourished, healthy man of fair intelligence, but illiterate.   The following was his written account of the concussion :

'I was shoeing a horse 8 days ago, when a shell Bust above me knocking Both of us Down, and another Burst a Bust above me and that is all that is what come to my memory, when I come to myself and how long I was unconious I Dont know yet only I feel splendid now only that my speach is gone, of cours I was hard of hearing but it has come alright now but still I am content I might have been worst.   I am not much of a scholar, I cannot spell the words very Well.'

He did not utter a sound, nor speak in a whisper.   He could only appreciate simple questions.

He was admitted to the National Hospital on August 17, and during manipulation with a warm laryngoscopic mirror patient began to whisper, and further encouragement resulted in the complete recovery of the voice in a few days.

Case III.   P. R., aged 22 years.   Went out to France November, 1914, was quite well till March 12, 1915, when a shell burst over his head.   He was unconscious for about half an hour.   On recovery he found he was deaf and unable to speak.   He could think of words, but could not say them.   He felt dazed and frightened for some days, and still wakes up with a start at night.

He was able to write a good account of his experience, which is correct in the main.   He rapidly recovered hearing.

He was admitted to the National Hospital on March 25, and wrote the following account :

'I went out to France on the 3. 11. 14. and I was two days at Le Havre and then we went on to our 1st Batt.   When we arrived at our destination the regiment was in the trenches so we had to go in.   It was snowing hard and I felt it very cold.   This was at Givenchy.   We were relieved the following night and we went back for a rest.   The next place we went to was to just opposite Neuve Chapelle on the La Bassee Road and it was awful, the trenches were up to the knees in mud and water.   The first night was very quiet, but the following morning about 9 p.m. the Germans started shelling and continued all day, the next was the same, but about 1 o'clock the Germans were seen to be coming up in masses.   They got to within a distance of about twenty-five yards, then they turned.   They commenced shelling us again and they had another try about 3 o'clock but they did not get far.   One of the men on my left had the half of his face blown away and we had about ninety-two killed and wounded.   We got relieved after being in five days, then we went back for three days' rest. The next place we went to was Rue de l'Epinette and we had an awful time there just before Christmas.   We went into the trenches and we were up to our middle in water and in some places it would have taken you over the head. We were in these trenches for twenty-four hours.   There was nothing unusual happened and we got relieved by the Royal North Lancs., but we did not get far away, we had just got into our billets and were making some tea when the fall in went and we were told that the Germans had broken through the North Lancs.   We went away without any great-coats, and into the trenches

we went for other seventy-two hours, and if the Germans had attacked again we could not have fired a shot as we were hardly able to stand for the cold and with the wet kilts on our legs it was awful. We got nothing to eat except three biscuits that some of the men went out and got. When we came out of the trenches on Christmas Eve we looked all like old men and a lot of them had to be carried. We went back for a rest to (Nervaille ?) about thirty kilometres from the firing line for a month. When we came back again we went to La Bassee and had a pretty hot time there. The next place we were at was at that big fight at Neuve Chapelle when 472 guns bombarded the German trench for thirty-five minutes. At about 7 p.m. the word was passed along that we were to charge the German trench in front supported by the City of London Territorials. We got the trench all right and I got orders about 4 p.m. to go back to our own trench and bring along the belt-filling machine belonging to the machine gun. There was not a proper communication trench, there was a small dry ditch that ran out in the direction of the trench we had taken for a distance of 150 yards, the other 100 yards you had to come across the open. We got into our trench all right, and I got this box on my back and started back to the trench. I was just stepping out of the trench when a shell burst just over my head and I went down. When I came to my senses I was lying in our support trench where I had been carried by two of the men of the 4th Black Watch. One of them said something but I could not hear him and I tried to tell him so, then I discovered that I could not speak.'

On March 27 speech returned suddenly and spontaneously, and by March 29 he had completely recovered and talked well.

The above account illustrates how perfect the memory may be up to the time of concussion, and how complete the mechanism is for expressing the ideas in written words when that for spoken words is abolished.

Group III.   Temporary Loss of Memory under Physical and Psychical Stress.

A. L., aged 28 years.   Admitted to the National Hospital March 14, 1915, for *loss of memory from March* 1 *to March* 5.

He had been in France since Dec. 31, 1914, in the Remount Department of the A. S. C.

He had been continually exposed to the severest weathers, working for long stretches, and sleeping in rain and mud, soaked through, hungry, and generally wretched and aggrieved. Towards the end of February he was feeling just about done up, and he remembered jumping off a wooden step into a muddy road to go across this to a wood, and so to the horse lines. He was found wandering in this wood five days later, not knowing who or where he was and having no recollection of what had happened to him in the interim. He was put into hospital and sent home.

He felt well in himself, and was beginning to remember things that immediately preceded his loss of memory, and which he had detailed as above. He complained of a feeling of want of confidence in himself, and general shakiness. He had no other symptoms.

He was a sturdy, well-built man in good physical condition. Thoracic and abdominal viscera healthy. Of normal intelligence and emotional tone. *Query*, a veracious witness, though his story presented no obvious inconsistencies. Memory, except for the five days mentioned, was normal.

His speech, vision, and hearing were quite normal. There was no defect of the cranial nerves. His musculature was very well developed. There was a fine tremor of the extended hands, but otherwise nothing abnormal.

Sensory system and reflexes were quite normal.

The patient still professed to have no recollection of the five days period mentioned in the history.   He was otherwise well.

Group IV.   Tremors.

Tremor in some form is a most frequent accompaniment of nearly all forms of shock.   No useful purpose would be served by recording the numerous cases of fine tremor which have been observed, but the two following cases illustrate some unusual features.

Case I.   Peculiar rhythmic tremor like 'dog's chorea'.   F. D., aged 27 years. Went to France in January, and was quite well till April 26, 1915, when he was buried by a bomb explosion in the trench.   He was not unconscious.   A few hours later he began to cry, and his arms began to twitch.

On May 4 he was admitted to the National Hospital.   He had then whilst awake a constant rhythmic tremor of both arms just like a dog's chorea, and the muscles in action chiefly were the pectoral on both sides.   The movements could be inhibited by putting the muscles on the stretch.   After a period of rest in bed the movements entirely ceased, and by June 12 he was quite well.

Case II.   Return of athetosis (present in early life) produced by shock. H. G., aged 27 years.   When 5 years old he had poliomyelitis of the left leg. When 20 he had pneumonia, followed by paralysis of the right arm and leg with loss of speech.

He recovered, but never quite regained full control of the right hand.

In October, 1914, he was struck on the right shoulder with a shrapnel, but was not wounded.   After this he could not use the right hand well, and it gradually got worse, so that two months later he could not manipulate his rifle properly, and on January 13, 1915, he was sent home.

He was a well-developed man, and was quite normal except for some general weakness of the left leg as compared with the right, and for irregular movements of the right hand and arm.   The movements of the right hand were those seen in athetosis, and these movements went on apart from volition.   He had difficulty in releasing the grasp.

It is of course impossible to say that this was not present when he enlisted, and that he was able to cover up the defect sufficiently to execute the necessary drill, &c., but at the time he was seen in the hospital it would have been impossible for him to have performed the movements either quickly or accurately enough to escape observation.   His statement is quite clear on one subject, and that is that the inability gradually developed for two months before he was sent home.

During the six weeks he was in the hospital he rapidly improved, but the movements of the right hand could not be said to be perfectly normal.

In this case the stress was sufficient to bring into prominence the symptoms due to an old cerebral lesion.

Group V.   Unilateral Spasm of the Muscles of the Face and Jaw.

H. M., aged 23 years.   On May 13, 1915, patient was struck by several pieces of shrapnel on the right hand, forearm, shoulder, and on the right side of the nose at its base.   He was very dazed, but did not lose consciousness.   The wounds healed in a month.

About a week after being wounded he was operated on in order that a piece of shrapnel might be removed from his face.   On recovering from the anaesthetic he found himself unable to move the right side of his face or to open his mouth.

This condition, which was quite painless, had persisted since, and he had not eaten solid food or been able to take out his false teeth.   He had been fed through a rubber tube inserted between his teeth.

In all other respects he felt well.

He was admitted to the National Hospital on June 18, 1915, and his state was as follows :—

The patient sat up in bed gasping in a highly alarming manner, with his left face in a strong tonic spasm and his jaws tightly set.   All efforts to open his mouth were unavailing, so strong was the contraction of his masseters.   When asked, he was able to separate his teeth by an interval of about half a centimetre, but directly an attempt was made to insert a spatula in this space the jaw clenched tightly and did not relax.   The facial spasm increased in force with the clenching of the jaw.

He declared himself unable to breathe unless sitting up, and when made to lie down his neck was strongly retracted and set and he breathed violently through his clenched teeth and held his breath for as long as he could, assuming a purple tinge which was apt to be disconcerting until one was accustomed to it.

By the moral aid given by strong faradism and force applied to the jaw, it was possible to remove a filthy set of false teeth.   During this performance he uttered piercing shrieks and foamed and his rigidly held arms shook violently. Tears ran from his eyes, and he sweated profusely from his muscular exertion in resisting the attentions, well intended though they were, of the medical attendant.

When asked to close his eyes he was able to do so; in fact, the left eye was half closed in the spasm.   All tests revealed good power in both sides of the face.   The facial and jaw spasm would seem to have been voluntary.

In the intervals of this grotesque performance he lay back on the pillow, without any dyspnoea, but he induced an apparent difficulty in breathing at will.

Examination revealed no organic disease or injury in either nervous or other systems.

On the night following admission the patient slept well in the recumbent attitude.   Seen while asleep the face was at rest, the spasm of left face and of jaw coming on perceptibly some few seconds after waking, and only when he perceived the observer.

Attempts to force open the mouth called forth the same phenomena as on the previous night.   He had, however, eaten well of ordinary diet.

Recovery gradually took place and at the end of a month was practically complete.   Slight spasm was present only when examined.   Mentally he was much brighter.

The above cases have been selected as illustrating a few of the various manifestations of functional disturbance of the nervous system produced by the war.

It cannot be said that there is any other common factor.

The temperament and intelligence of the patients have varied greatly. The physical condition in some has been poor, but in others quite good. Worry, physical exhaustion, and its attendant depression have been factors in some cases.

It is not improbable that in some cases an organic lesion may have been present in the early stages and have been accompanied or followed by functional manifestations. The dread of returning to the conditions which have produced the symptoms is certainly a dominant factor in many cases, but even this is not present in all.

In conclusion, I would like to take this opportunity of acknowledging my indebtedness to my house-physician, Major Walshe, not only for the great care and attention he paid to these patients, but also for the records of their condition.

ACUTE HODGKIN'S DISEASE, WITH INVOLVEMENT OF INTERNAL GLANDS AND RELAPSING PYREXIA

By T. H. WHITTINGTON

THE following case is worthy of publication for three reasons. In the first place the general course, amongst other peculiarities, presented a combination of an acute onset in an 'internal' form of the disease with a relapsing pyrexia and signs and symptoms chiefly abdominal. Secondly, it formed an interesting problem in diagnosis, and the endeavours to solve this gave rise to much speculation, for the case deceived the very elect. Finally, at the post-mortem many interesting pathological features were discovered, and only then was the diagnosis settled.

In MacNalty's study of 'Lymphadenoma with Relapsing Pyrexia' (this Journal, October, 1911) of 32 cases there were eight without enlargement of the superficial glands. Only two of these had a shorter duration than the case here reported. One, a male, aged 23, with involvement of mediastinal glands, spleen, liver, and kidney, died in five weeks; the other, also recorded by Dreschfeld, had enlargement of the mesenteric and bronchial glands, the liver and spleen, and lived seven weeks. The others lived periods varying from four to fifteen months.

Description of Case.

Onset. Private L., aged 19, reported sick on November 21 for 'frost-bite' occurring in the trenches in Flanders. He was admitted to a Base Hospital for this complaint on November 23.

On admission, the patient looked pale and complained of pains in toes and soles of feet, but nothing abnormal was seen in these parts. The temperature and pulse-rate were normal. He was badly constipated and therefore was given a strong aperient pill. Two hours later he complained of severe abdominal pain, mostly in the right side. The abdomen was then tender, held rigid, but not absolutely so, and moved slightly with respiration. The patient's temperature and pulse-rate were raised, and during the next few hours he vomited two or three times.

The appearance of the case was suggestive of peritonitis, but no localized tender or dull spot could be made out, and the patient's general condition being good the case was carefully watched without resort to operation.

Previous history. The patient was a recently enlisted soldier and was not inoculated against typhoid. He had been quite well until the onset of pains in legs. There was no history of previous illness except two attacks (at 14 and

16 years of age) suggestive of recurrent appendicitis. He had never been abroad. No family history of tubercle, syphilis, or blood disease could be obtained.

Subsequent course. The following day, November 24, the temperature remained up at 103° to 104° F.; the patient was lethargic and pale, with a soft and relatively slow pulse.

His abdomen was now distended, slightly tender all over, and still rather rigid. The tongue was dry with brown fur. A leucocyte count showed a leucopenia of 3,500. During the next two days he remained about the same, except that his abdomen became tumid and less tender.

On November 27, owing to the above symptoms and signs, he was sent to the Infectious Diseases Hospital as probably 'enteric fever', and came under my charge. His condition was as described, but the following additional facts were noted. The patient was very pale, with a rather 'renal' appearance, and complained much of headache. There was occasional muttering delirium, with picking at the bed-clothes. The pulse was very soft and occasionally dicrotic. There was marked tenderness in the left hypochondrium and left lumbar regions of abdomen, and this tender area was dull on percussion. The spleen was not felt, but this dullness appeared splenic and reached down towards the umbilicus four fingers breadth below the costal margin. The heart sounds were good and normal. There was diminished resonance over the lower lobe of the left lung behind, coming round to blend with the afore-mentioned dullness. No spots were seen. No enlarged glands were felt anywhere. The stools were fluid and yellow, with no slime, blood, or curds. The urine was quite clear, no pus cells or casts were found, and there was no bacilluria, but a trace of albumen was present. The serum gave no agglutination with the Bacillus typhosus or with either of the paratyphoid bacilli.

The diagnoses which so far had been suggested at various times were acute peritonitis, recurrent appendicitis, and typhoid fever, the last being especially favoured. Acute lymphatic leucaemia was also suggested.

During the next six days the patient remained about the same, but the abdominal distension got much less, enabling the firm and slightly tender spleen to be felt easily.

On December 2 a leucopenia was still present—2,200 white cells per c.mm.— and the haemoglobin was only 52 per cent. of the normal. A blood culture made into a bile salt medium proved sterile and the agglutination reactions were again negative.

From December 2 to 5 the temperature came down in a 'step ladder' manner and at the same time the patient rapidly improved; there was no distension of the abdomen and the spleen grew much smaller. Treatment had consisted in tepid sponging and the administration of a fluid diet, and constipation had been treated by enemata. The case was considered for the time being as one of typhoid fever. However, on two occasions both stools and urine failed to grow the typhoid bacillus or either of the paratyphoid organisms. The patient continued apyrexial for nine days, being quite bright and cheerful, and on December 31 commenced to take a little solid food. The temperature then quickly went up by steps, and this rise was associated with listlessness, headache, a dry furred tongue, a tumid abdomen, enlargement of the spleen, and some loose motions, and the pulse was soft and compressible. In other words, the whole condition was much like a relapse in typhoid fever, and it was feared that this had been caused by injudicious dieting. The patient, however, showed a marked pallor unlike a typhoid case, no spots were seen during the 'relapse' and a second blood culture proved negative, and for the third time the serum failed to show agglutination with bacilli of the enteric group.

By December 30 the patient had steadily improved after seven days' normal temperature. He was not nearly so pale, was bright and cheerful, and with his thin skin and blue eyes had a look of the 'sanguine' tuberculous type.
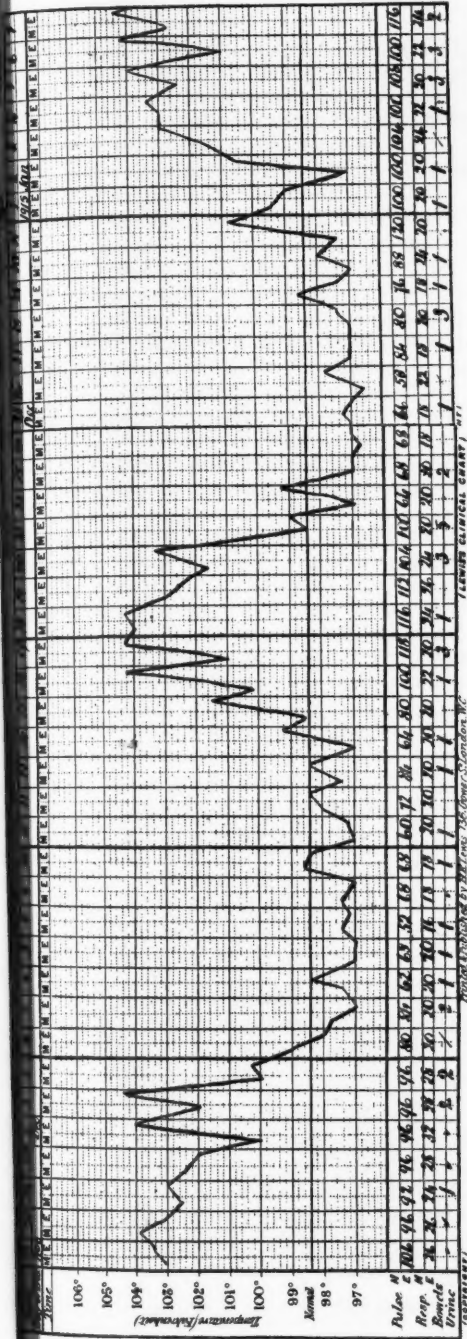
FIG. 1.
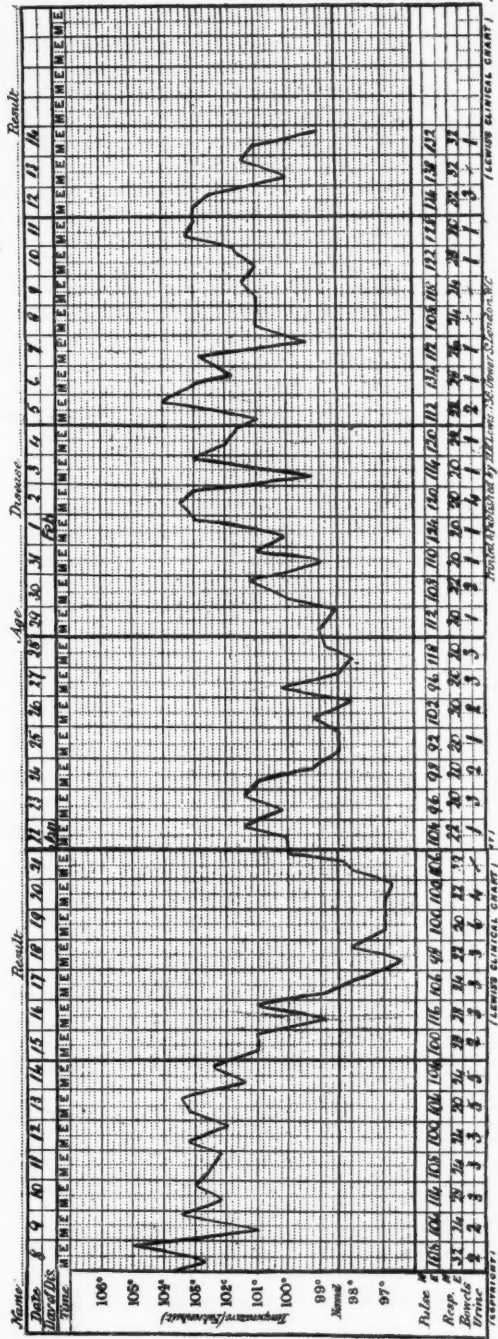
FIG. 2.

H 2

During this time the spleen had rapidly contracted until at this date it was no longer palpable.

On the evening of December 31 he again became listless and pale ; the next day these features were very noticeable, and he again complained of pain in the toes and soles of the feet. Coincidently with this the temperature went up and the spleen again rapidly enlarged. The temperature soon came down, only to rise again quickly on January 4. There was then a rapid increase in pallor and a still greater enlargement of the spleen. The abdomen was full and the liver was now made out to be slightly enlarged. The pulse was very soft but not dicrotic. There was diarrhoea and the stools were almost 'typhoid' in character. Patient later complained of sore throat, but nothing was found and there were no enlarged glands in the neck. A blood examination at this time showed 3,000 white cells and 3,600,000 red cells per c.mm. A differential white count showed the following percentages : polymorphonuclears 80 per cent., lymphocytes 15 per cent., large mononuclears 5 per cent. No eosinophils or nucleated red cells were seen and no parasites were found.

He was seen by several consultants and the diagnoses suggested were : a typhoid relapse, a splenic anaemia, and tuberculous peritonitis. The difficulties of the case at this time are shown by the possibilities also discussed, viz. Hodgkin's disease, Malta fever, kala-azar, congenital syphilis, and septicaemia. A blood culture made into broth was sterile and the agglutinations were again negative. The blood count was repeated a few days later and again showed a leucopenia, and stool and urine cultures were again negative as regards bacilli of the typhoid group.

The temperature came down satisfactorily, and by the 20th the patient was better, although rather emaciated with a weak pulse, and haemic murmurs were heard at the base of the heart. The spleen also was smaller, but still palpable and firm. Other than the spleen there were no glands to be felt anywhere. On January 21 he was given a mixture with arsenic and iron, and he had this for a little over a fortnight. On January 29 the temperature again began to go up, and the abdomen got markedly distended. This time there was free fluid in the flanks and lower part of the abdomen. The splenic dullness again increased and the pallor again became marked. There appeared to be a very indefinite mass felt on firm palpation above the umbilicus. Operation for tuberculous peritonitis was strongly advised by one of the consultant surgeons who saw him at this time and who thought that the above mass was matting of the omentum. Operation was, however, not performed as the patient was getting rapidly very weak.

A blood count again showed marked leucopenia, the relative numbers of the white cells being normal except that only two eosinophils were seen. The red corpuscles were down to 3,000,000 and the haemoglobin down to 35 per cent., giving a colour index of about 0·5.

By February 8 the patient was very emaciated with a gradually increasing jaundice of an obstructive kind, and there was some cutaneous mottling of a purpuric nature. Diagnoses which now suggested themselves were a splenic anaemia (especially Banti's disease), tuberculous peritonitis, or obscure malignant disease.

By February 13 the patient appeared to be dying. He was markedly jaundiced, very emaciated, and weak, and the abdomen was distended. The general appearance was that of malignant disease in the abdomen with obstructive jaundice. The white-cell count had risen to 15,000, this probably being a rise associated with a dying condition, as death supervened thirty-six hours later, just twelve weeks from the apparent onset.

Diagnosis and Discussion.

The most noticeable features (considering the ultimate diagnosis) and the ones which led observers astray were as follows :

(*a*) The acute onset with symptoms and signs suggestive of peritonitis.

(*b*) The subsequent remarkable resemblance of the case to typhoid fever. This was evidenced by the lethargy and quiet delirium, the soft, compressible and rather slow pulse, the 'typhoid' tongue, the tumid abdomen and the enlarged spleen, the leucopenia, the supposed 'relapses', and the diarrhoea with suggestive stools.

(*c*) The general resemblance to an acute infective fever.

(*d*) The relapsing course in which there were not only relapses in pyrexia but also a curious periodicity of symptoms and signs. At the onset of and during each pyrexial period there was rapid wasting and increasing pallor and a regular and marked increase in the size of the spleen. This rapid alternate enlargement and contraction of the spleen seemed a noticeable feature of the case.

(*e*) The signs suggesting portal obstruction.

(*f*) And lastly (and very important) the entire absence of enlarged external glands.

The above facts are some excuse for the failure to make an accurate diagnosis during life.

Hodgkin's disease was discussed in connexion with the enlargement of the spleen, but the above facts led us off the track. The patient was of the usual age for the disease and it is more common in males than in females.

The onset was remarkable. Cases have been described in which enlarged external glands were present for a long time, or in which the process appeared 'latent', and which then became suddenly acute in association with a bursting out into activity of the pathological processes in the glands. But when the deep glands only are involved the onset is usually insidious, and the acute onset in such a case as this one seems very exceptional. Jaundice and ascites are commonly associated with the abdominal type of Hodgkin's disease. In at least 70 per cent. of the cases enlargement of the superficial lymph glands is the first thing noticed, and in the great majority the cervical glands are most affected. The entire absence of enlarged superficial glands in a case showing the relapsing fever of Pel and Ebstein is therefore most unusual. It has been suggested that these pyrexial periods may be due to the presence of some secondary infection, and it should be noted, therefore, that besides the two blood cultures made into a bile salt medium a blood culture was made into broth at the commencement of one of the periods and that all the cultures were found sterile.

As regards the blood cells, the leucopenia and the scarcity of eosinophiles are possibly unusual features. On the other hand, the very marked chlorotic anaemia is often seen, but the rapidity with which the haemoglobin (as estimated

by Sahli's apparatus) reached as low as 35 per cent. is unusual, and with other facts seems to be a sign of the very severe form taken by the disease in this case.

The resemblance to *typhoid fever* has already been mentioned.   The onset, the absence of spots, the rapid general recovery as soon as the temperature was normal, and the completely negative findings in the laboratory were the chief points against this diagnosis in the early stages, while the later stages were quite unlike enteric fever.

In *Banti's disease* the probable source of the trouble is in the spleen itself, and the alterations in the size of the spleen suggested an affection in which the spleen played a leading part.   Also, the blood examination revealed a condition quite typical of this malady, namely, the secondary anaemia with a very low colour index and a leucopenia with no special change in the differential leucocyte count.   Finally, the enlargement of the liver with the development of ascites and jaundice added decidedly to the resemblance of the case to this disease.   In such a diagnosis, however, there were many obvious difficulties, namely the onset, the rapid course and the general appearance, and the fever.

Tuberculous peritonitis was suggested by the tumid feel of the abdomen, there being present some generalized distension, and a soft elasticity on palpitation.   Also, later there was some ascites and it was thought that rolled-up omentum could be felt.   An acute onset is not infrequent in this disease, and a high temperature is then common.   The patient, too, appeared of a tuberculous type.

Against this diagnosis were the general course, with relapses, the enlargements of the spleen, and the absence of signs of tubercle elsewhere.

The leucopenia and the subsequent course were against the following earlier suggestions, viz. acute peritonitis, appendicitis, septico-pyaemia, and lymphatic leucaemia.

The predominant part apparently taken by the spleen, the resemblance to some infective fever, and the fact that the patient was a soldier suggested at one time, in the search for a diagnosis, such diseases as Malta fever, kala-azar, and relapsing fever, affections not usually thought of in dealing with Hodgkin's disease.   Against these possibilities were the locality and previous history, besides the clinical and laboratory findings.

Post-mortem.

The body was very emaciated and deeply jaundiced.

Abdomen.   A large amount of free clear yellowish fluid was found.   The omentum was normal except for a very diminished quantity of fat, and it showed no matting together.

The rest of the peritoneum appeared normal—no tubercle or carcinomatosis being present.

The intestines and mesenteric glands appeared normal.   The spleen was at least three times the normal size, of a dark slaty-blue colour and decidedly firm and hard and not friable.   On its surface were seen scattered yellowish-white spots about the size of a pin's head and slightly raised.   There was no peri-

splenitis. On cutting the spleen open similar areas, in some cases larger, were seen scattered all about, and being yellow stained seemed like points of pus. They were found, however, to be fairly firm like little pieces of firm yellow fat. The structures in the hilum of the spleen appeared normal. The liver was a little enlarged but otherwise appeared normal. A gland in the portal fissure was enlarged and cut firm and hard, but it was quite discrete. It seemed to be pressing on the hepatic duct before this joined the cystic duct and the hepatic duct appeared dilated. The gall-bladder was full, but the dilatation was not definitely more than might normally occur. It contained viscid mahogany coloured fluid. The bile duct seemed a little dilated and appeared to have been pressed on by some enlarged glands behind the pancreas. It could, however, be easily separated from them and these glands were quite discrete. The kidneys were apparently normal and did not show any nodules, and both suprarenal capsules were normal to the naked eye. On attempting to remove the left kidney some very interesting abnormalities were found. On tracking down the left ureter it was found to enter a large irregularly lobulated hard mass—discovered to be retroperitoneal glands—extending from the level of the left renal artery down to the bifurcation of the aorta. This mass had prolongations downwards along the common iliac and iliac arteries of the left side and for a short distance along the common iliac on the right. The aorta and left ureter were enclosed in this mass, but did not appear to have been pressed on unduly. On dissection the glands were found to be regularly oval or rounded, smooth and discrete, and apparently not obstructing ureter, arteries, or veins or encroaching into surrounding structures. They were creamy white in colour and cut firm, and some showed on the cut surface bulging areas between restraining connective tissue.

Nearly all showed a mottled appearance due to haemorrhagic areas near the capsule. There was no growth at all through or outside the capsule and the glands appeared typically lymphadenomatous. The testes were normal. Some enlarged glands, one about the size of a walnut, were also found behind and above the neck of the pancreas, and were like those above described. The lungs, heart, and pleurae showed no obvious abnormalities. The tracheal and bifurcation glands were decidedly enlarged, hard, and discrete, cut firm and showed mottling with areas of congestion, and were of a similar nature to those already described. They did not appear to have pressed on surrounding structures. Some old calcareous and caseous glands with sooty deposits were found adherent to bronchi at the root of the right lung and appeared to be old tuberculous glands. Some enlarged glands were found just behind and below the inner end of the clavicle on each side, one on the left being the size of a walnut. They also appeared lymphadenomatous like the others. Otherwise the cervical glands were not enlarged. Portions of the retroperitoneal, portal, thoracic, and subclavicular glands and spleen were kept for histological examination. They were found to show the typical appearances of Hodgkin's disease. These glands showed proliferation of the endothelial cells and of the reticular tissue, in the meshes of which numbers of moderately large lymphoid cells and the characteristic giant cells or 'lymphadenoma cells' were evident. These were nearly all of the mononuclear type, the big nuclei showing pale blue indefinite staining with deeply stained dots scattered about (nucleoli and chromatin granules). No giant cells with the 'horseshoe' arrangement of nuclei were seen. The proliferation of the connective tissue did not seem far advanced in any of the glands examined, and this fact, in conjunction with the presence of haemorrhagic areas, suggested (apart from the clinical evidence) that the disease was rapid and acute in this case, and not, as is usual, slow with progressive and finally marked increase in the connective tissue.

One can say that the mass in the abdomen did not appear old, and that the case was probably not one of the 'latent' variety with a subsequent bursting out into activity.

The indefinite mass felt during life and supposed at one time to be matted omentum was probably this mass of retroperitoneal glands, and this mass by pressure on nerves possibly accounted for the pains down the limbs and in the feet and toes for which the patient went sick and which he again had while in hospital. Such symptoms do not appear uncommon in cases of the abdominal variety. That a case of Hodgkin's disease should first come under observation for this complaint and be diagnosed 'frost-bite' must certainly be uncommon. The associated circumstances and the prevalence of 'trench foot' amongst the soldiers at the time accounted for his being sent down to hospital with this diagnosis.

It was interesting to find that the supposition of an enlarged gland in the portal fissure was confirmed, but more interesting to find that this enlargement was due to lymphadenoma.

Almost all the symptoms and signs were now explained except the acute onset, the toxic symptoms, and the fever.

The whole aspect of the case seems to support the view that Hodgkin's disease is due to some infective organism, which in this case was particularly virulent, and which had its chief habitat in the retroperitoneal glands and spleen.

PYELO-NEPHRITIS WITH GLYCOSURIA

By J. H. RYFFEL

(From the Laboratory of Clinical Chemistry, Guy's Hospital)

General Account.

THE patient, a man aged 32 years and 6 feet in height, was employed as stoker at a gas factory. He stated that he had been in good health until the beginning of 1914, when for six months he was subject to recurrent attacks of diarrhoea, the motions occasionally containing blood. Then his legs became oedematous, and three weeks later he was admitted to Guy's Hospital on July 20, 1914.

On admission his lower limbs and the lower half of his body were oedematous. He complained of headache and of some impairment of vision. The retinae showed some optic neuritis but no albuminuric retinitis. Maximum systolic blood-pressure was 110 mm. Hg; pulse 72 to 80, respirations 20 to 24 per minute, temperature 96° to 98·6° F. There were no abnormal signs in the heart and lungs. The urine of the first few days averaged about 1,500 c.c. daily of specific gravity 1,020, and contained albumin about eight parts per 1,000, granular casts, much pus, and a little blood.

He did not sweat naturally, and responded only feebly to hot-air baths and hot packs, so that these were ultimately discontinued. He did not suffer from diarrhoea; in fact, there was usually slight constipation, which was easily controlled by the use of 'Pulvis Salium'.

From the 59th day after admission till the 100th day he had slight recurrent pyrexia, the highest temperature recorded being 101° F. After that the recorded oral temperature was consistently subnormal, probably because the patient habitually had his mouth open.

On the 57th day his legs were acupunctured, with the result that the oedema diminished considerably, and whereas until then the daily volumes of urine had rarely been above 1,500 c.c., from that day they showed a progressive increase, so that on the 60th day the volume was 4,400 c.c., and on the 73rd day a maximum was reached with 9,530 c.c. Polyuria continued with a diminishing tendency, but it was not till the 168th day that the volume became less than 2,000 c.c. From the 67th day sugar was found to be continually present in the urine. After the effect of diabetic diet had been tried, the patient was given a light full diet with as little salt as possible and the glycosuria gradually diminished, having completely disappeared by the 250th day.

With the advent of polyuria the blood disappeared from the urine, but there were still a considerable number of pus cells and a few granular casts. No organism was found in a catheter specimen of the urine on the 88th day, but on the 133rd day numerous chains of Streptococcus pyogenes longus were found. From these a vaccine was prepared which was given subcutaneously at intervals of a week to ten days in doses increasing from 2·5 millions to 150 millions. On the 207th day streptococci were still present in the urine. A fresh strain was

prepared and the vaccines given from the 220th day were from this new material.

Whereas previously the patient's limbs had always been dry, on the 200th day it was noticed that he was sweating appreciably. Since then natural sweating gradually returned, until he appeared to sweat more freely than the average normal.

From the 203rd day the patient underwent a course of massage and muscular exercises, and from the 210th day he was given urotropin 30 grains and acid sodium phosphate 45 grains daily. Improvement set in, so that the patient was discharged on April 14, 1915, the 269th day, with only slight oedema of the legs and less than one part of albumin per 1,000 in his urine.

Fortnightly doses of vaccine were continued for another two months. After the first fortnight at home the albumin had fallen to 0·1 per 1,000 and there was no oedema. Urotropin and acid phosphate were discontinued, but recommenced three weeks later as the pus had increased, the albumin had risen to 1 per 1,000, and there was frequency of micturition. A fortnight later the albumin had again fallen to 0·25 per 1,000.

Ten weeks after discharge the patient returned to work, but not as a stoker. At the end of October, 1915, there was no oedema, the systolic blood-pressure was only 110 mm. Hg, the urine contained a minute trace of albumin and an occasional pus cell, although the urotropin had been omitted for a fortnight, and the patient was in general appearance perfectly well.

Glycosuria.

The presence of sugar in the urine, as shown by reduction of Fehling's solution and by the formation of dextrosazone, was first noted on the 67th day, a few days after the commencement of the polyuria. The amount of sugar was at first about 0·5 per cent. Exceptionally on the 98th day the output for the twenty-four hours was 69 grammes or 1·5 per cent. in the urine. The influence of diet, additional urea, and diuresis on the glycosuria was tried with the results shown in Chart I. The output of sugar showed a tendency to diminish throughout the series. Correcting for this the change from a diet free from carbohydrate to a full allowance of carbohydrate had very little effect, while theocin by causing an increase in the output of urine also increased the output of sugar.

These results show that the glycosuria was renal in type. Moreover, the sugar in the blood, determined by Dr. Graham on the 171st day by Bang's method, was 0·116 per cent., a normal amount, so that there was no hyperglycaemia to account for the glycosuria.

Functional Activity of the Kidneys.

From the 45th to the 54th day Dr. Heaton tested the response to additional sodium chloride, urea, and creatinin given by the mouth.

With the patient on a low chloride diet 10 grm. of sodium chloride produced very little response, the day's output of sodium chloride being increased from 0·39 grm. to 0·46, 0·43, 0·41 grm. respectively for the next three days.

CHART I.
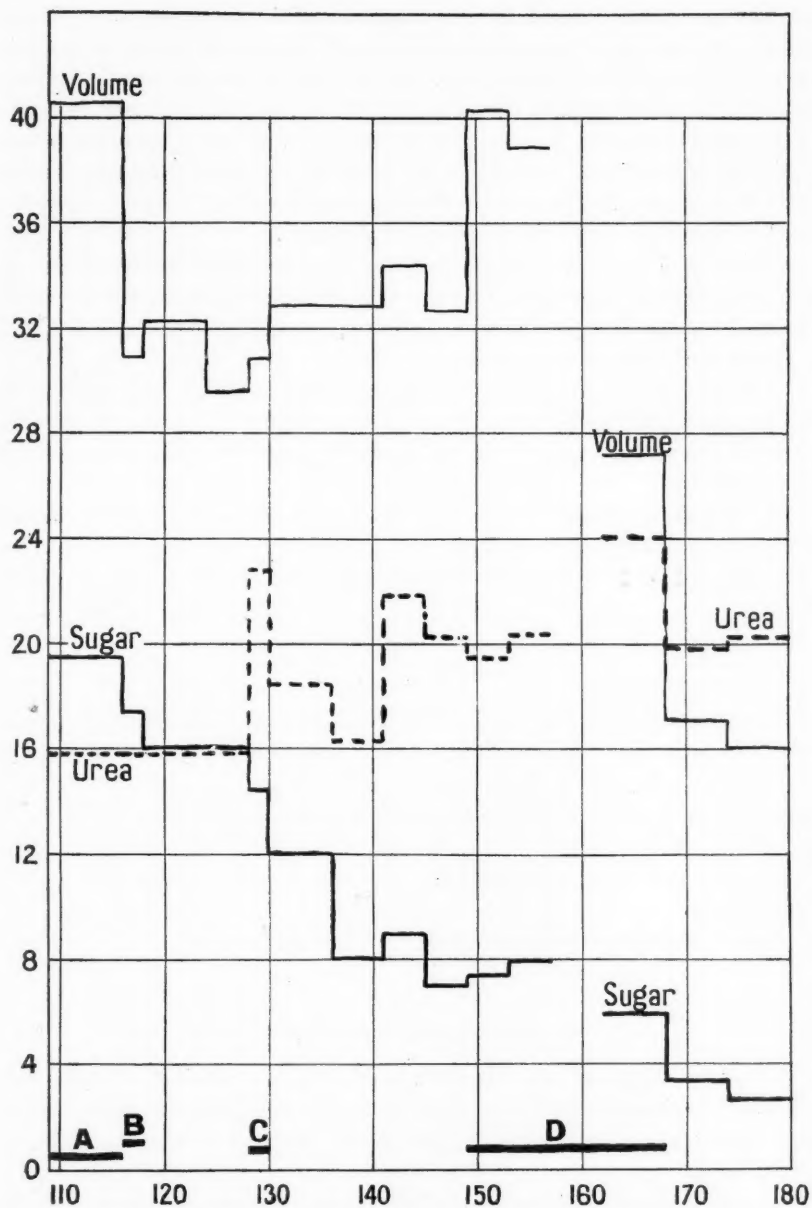
A. Diabetic Diet   C. 10 G. Urea daily
B.   "   + 180 G. Bread   D. Theocin & Digitalis given
Rest. Light Full Diet

One dose of 20 grm. of urea caused a rise in the output of urea from 20 grm. to 30 and 24 grm. for the next two days.

For the determination of the response to creatinin the output was estimated in six hourly periods, after a dose of 1·5 grm. of a preparation rich in creatinin, according to the method of Neubauer. The average output of creatinin previous to the dose was 0·33 grm. in six hours. This rose to 0·83, 0·61, 0·49, 0·35 grm. for the next four consecutive periods of six hours, so that 50 per cent. of the additional creatinin was excreted in six hours and practically all was excreted in eighteen hours. In the normal the excretion would be complete in twelve hours, with a higher proportion in the first six hours.

There was, therefore, a slight delay in excreting urea and creatinin. As there was marked oedema at the time, this is to be attributed mainly to the abnormally large amount of fluid in the body, not to any appreciable failure in excretion on the part of the kidneys.

Urea in the blood was determined by Ambard's method using hypobromite. The results were : on the 45th day 0·23 grm. of urea per 1,000 c.c. of blood, on the 136th day 0·23 grm., on the 267th day 0·35 grm. These figures are within normal limits.

Clearly then the case belonged to the type described by Widal and Javal and others in which there is oedema with diminished power to excrete chloride, while the excretion of urea and other waste products differs little from the normal.

The Blood.

Samples of the blood were taken in all five times up to the 200th day. On each occasion the blood clotted slowly and the serum which separated was milky, the milkiness being due to minute particles which did not separate on centrifugalizing. In fact, the cloudiness appeared to be due to the presence of a lipoid 'sol' analogous to that found in some cases of diabetes. The blood was again examined on the 267th day and found to yield a serum which was normal in appearance.

The Wassermann reaction of the serum was negative.

Response to Treatment.

The daily values of the albumin : urea ratio, the volumes of urine and output of albumin and chloride expressed as averages for groups of days, and the body weight taken every second day, are shown in Chart II from the 130th to the 268th day.

As a result of the draining of the legs on the 57th day and the subsequent polyuria there was little oedema for a time, but in spite of the continuance of the polyuria the oedema gradually returned. The legs were again acupunctured on the 136th day ; the head of the bed was raised and the patient sat up for

CHART II.

Volume

Weight

Albumin

Albumin
Urea

Na Cl.

DAY 130 150 170 190 210 230 250 270

A B C D E F G H

25 M 5 M 10 M 10 M 25 M 25 M 30 M 50 M 50 M 100 MS 50 M 60 M 60 M 100 M 140 M

Na Cl grammes per diem --- Albumin ×10: Urea Albumin grammes per diem Volume in C.C. 100 Weight
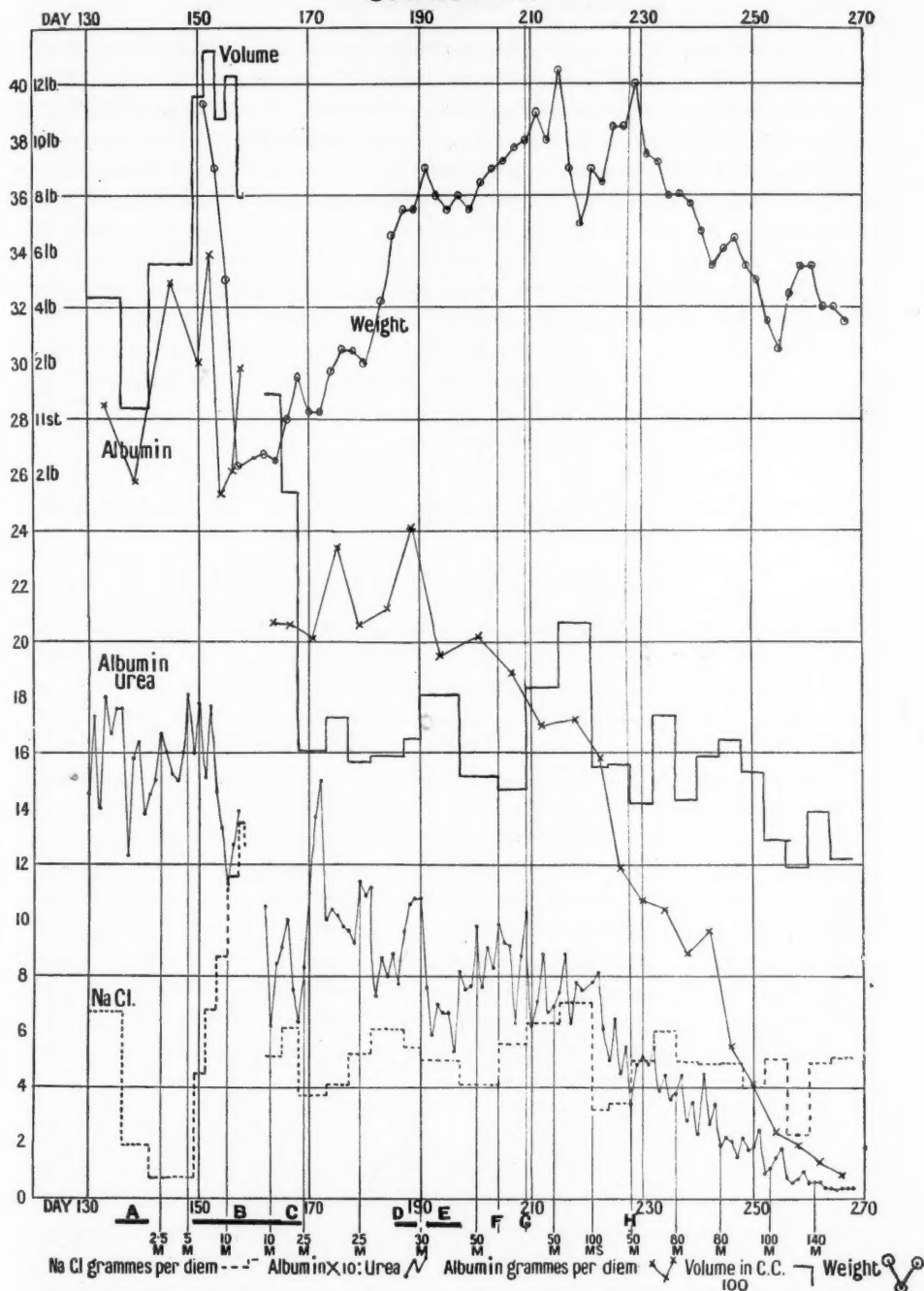
A. Legs drained.
B. Theocin and digitalis given.
C. Theocin and digitalis given in smaller doses.
D. Theocin given.
E. Urea given 10 grm. daily.

F. Massage and exercises begun.
G. Urotropin and acid phosphate begun.
H. Exercises increased.
M. Vaccine in millions.
MS. Vaccine in millions sensitized.

part of the day. The legs drained freely for several days, but the chloride in the urine fell considerably and the oedema rapidly returned. From the 149th day he was given theocin, sodium acetate 12 grains with tincture of digitalis 30 minims daily; he was kept in bed, and the head of the bed was no longer raised. For the first nine days the daily volumes of urine were considerably increased and there was a progressive increase in the output of chloride and loss of oedema and of body weight. After fifteen days the diuretic effect had considerably diminished and the body weight was stationary, although the oedema had not entirely disappeared. The theocin was diminished for three days and then omitted altogether on the 168th day. The volumes of urine fell to about 1,600 c.c., or about half what they had been before the diuretic was employed, and there was a distinct and permanent diminution in the albuminuria in the same interval. The oedema slowly returned with a corresponding slow rise in the body weight. The continued use of theocin appears to have destroyed the power of response to this drug for a considerable period afterwards, as the drug was again given for three days from the 187th day without any appreciable result.

Vaccine treatment was started on the 143rd day, or six days before the administration of theocin. The immediate effect of the injection on the albuminuria was irregular, there being a rise of the albumin : urea ratio on the day of injection on eight occasions, a fall on five, and no change on two, in a total of fifteen injections. The diminution in the albuminuria from the 149th to the 168th day is to be attributed mainly to the successful use of the diuretic. After this there was a period of stagnation with a rise in weight till the 204th day, when muscular exercises and massage were started. Then urotropin and acid phosphate were given from the 209th day. From the 199th day to the 218th, consecutive periods of five days yield average values for albumin $\times 10$: urea of 8·48, 8·64, 7·8, 7·42, and after this the albumin fell continuously, so that the diminution of the albumin dates from the 204th day when urotropin was given. The patient's weight reached a maximum for the period under consideration on the 215th day with 11 st. 12·5 lb. (far less than before the first tapping, when it reached 13 st. 12 lb.), but it was not till the 228th day, when the amount of exercise given to the patient was increased in accordance with his capacity, that a progressive fall in weight and diminution of oedema set in. From this point his progress was uninterrupted.

Summary.

The case was one with an unusual combination of symptoms. With oedema of a distribution not usually associated with renal disease, he had dry skin, marked albuminuria, pus and casts in the urine, and lipaemia. After an interval polyuria and renal glycosuria developed. No evidence was obtained of impairment of renal function except as regards the excretion of chloride, and there was some response to diuretics. The amount of pus in the urine

was such as to justify the supposition that organisms were present in the urine. These were ultimately found and identified as Streptococcus Pyogenes longus in pure culture. The case was treated as one of infection of the kidneys, vaccines and later urotropin being employed. The combination was ultimately successful. As the blood-pressure was low and the patient had been inactive for a long period, progressive muscular exercises were employed in the later stages with beneficial results.

In conclusion I desire to thank Dr. Fawcett, Dr. Hale White, and Dr. Lauriston Shaw, under whose care the patient was at various stages of his career, for the opportunity of investigating the case, and to thank Dr. Eyre for the bacteriological work, and Dr. Heaton and Dr. Graham for the determinations previously mentioned.

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PARATYPHOID FEVER—A STUDY OF FATAL CASES

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With Plates 6–11

FATAL cases of paratyphoid fever are sufficiently uncommon to be worthy of record. The following account is based on two cases of paratyphoid A and fifteen cases of paratyphoid B with their post-mortem appearances.[1]

Although in general paratyphoid is a reduced image of typhoid fever, the occurrence of severe and fatal cases shows that it has potentialities for greater mischief, and that under conditions favouring it the disease might break out in severe epidemic form—a consideration which bears upon the question of preventive inoculation.

The clinical picture of the severe case conforms so closely to that of typhoid that a complete description of the signs and symptoms would serve no purpose. A certain diagnosis between the two must be based on the laboratory findings.

The onset calls for no lengthened description. In only eleven of the cases could it be accurately noted. Abdominal pain and diarrhoea were the most frequent, occurring at onset in nine and eight cases respectively; together with vomiting they were the features of three cases which had a sudden onset. Headache occurred in six, cough in three, and epistaxis in two cases. The tongue resembled that found in typhoid.

In thirteen cases spots were present, and in some instances they were of larger size and less regular outline than those of true typhoid.

Abdominal distension is often noticeable by its absence, while in the toxic patients the 'typhoid state', with its wandering and low delirium, is less often a feature.

Respiratory System.

Rapid breathing is evidence, but not, like the pulse, a constant feature of a severe infection. In some cases it is not associated with definite signs in the lungs, and would appear to be the effect of the toxaemia on the central nervous system; a variability in the rate is suggestive of this type.

In four out of the seventeen cases the respiratory manifestations were so definite as to be a presenting feature of the clinical picture, and these cases are worth further consideration.

[1] Previously referred to in outline in *British Medical Journal*, Nov. 13, 1915, and *Proc. Roy. Soc. Med.*, Dec. 1915.

Massive Pneumonia.—Case 4, *Chart I.* Developed the signs of lobar pneumonia at both bases (chiefly the right) on the sixth day of the disease; became delirious and died four days later, that is, on the eleventh day of the disease. At the autopsy the right lower lobe was solid and sank in water, and there was a little lymph on the pleurae and between the lobes. The left lower lobe was congested. There was early typhoid ulceration of the small intestine.

CHART I.

Was this pneumonia caused by paratyphoid or a supervening pneumococcal infection? It has been shown that lobar pneumonia can be caused by Bac. typhosus and paratyphosus alone, though probably more often the pneumococcus is in association. In this case there was an abrupt beginning to the lung invasion, as the record of the temperature, pulse, and respiration shows. There was no sputum, and no culture from the consolidated lung was made.

Case 3, *Chart II.* Massive pneumonia with cavity formation from necrosis. The respiration rate was high from the time of admission (eighth day) to hospital and the colour dusky. On the fifteenth day the resonance and breath sounds were impaired at both bases posteriorly; on the twenty-third day these signs were more marked, and as the 'spiked' temperature suggested the possibility of suppuration the chest was punctured, but without result. A small quantity of saline was then injected from a syringe into the lung, sucked back, and put into broth, but with a negative result. On the twenty-seventh day there were many crepitations heard over the lungs posteriorly; the breathing was about forty and increasingly embarrassed. On the twenty-ninth day the patient died. A comparison of the foregoing signs with the post-mortem findings brings out once more what inadequate information physical examination may afford of the actual condition of the lungs. We all knew from the patient's general condition that the lungs were more extensively involved than the physical signs denoted. At one time the possibility of concurrent tuberculosis came to mind, and the sputum was examined for tubercle bacilli twice with negative results.

The necropsy showed definite ulceration of the small intestine. Both lungs were almost completely consolidated, though the left was more affected than the right. Some thin lymph covered the apex of the upper lobe of the left lung. The anterior third of the upper lobe was aerated, though congested and oedematous. The posterior two-thirds, with the exception of a thin marginal strip, was solid. In this solid area the tissue was red-brown in colour and absolutely airless. Along the posterior margin there was a cavity $1\frac{1}{2}$ in. $\times$ $\frac{3}{4}$ in. with well-defined wall which contained a grey-white débris. The lower lobe was also completely consolidated with the exception of small marginal areas, and there were many small white patches and strands of grey hepatization. There were some twelve
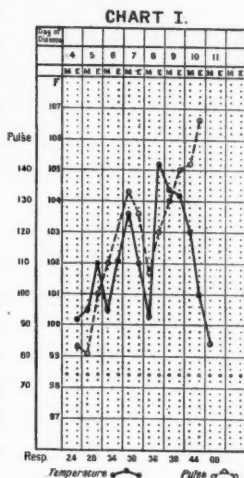
to fifteen foci of breaking down lung tissue in the solid portion, suggestive of commencing cavity formation. Microscopically, the section showed intense packing of the lung tissue with small round cells, with complete obscuration of the alveolar arrangement in places. In addition, there was a considerable exudate of lymph and evidences of proliferation of the fixed connective tissue cells. The whole picture was one of broncho-pneumonia, which had advanced in places to wide necrosis and abscess formation (Plate 6).

There was an abscess of the lung in another case (13), which will be referred to later.

The remaining two cases with prominent respiratory manifestations were examples of broncho-pneumonia, and in one of them (2) there was an infarct with a pleural effusion.

Circulatory System.

A pulse slow in proportion to the temperature is one of the most characteristic features of paratyphoid, and the bulk of the cases have a rate lying between 70 and 90. In the severe cases, however, the pulse is rapid, and there is no single sign so significant and prophetic. If the pulse is recorded on the same chart as the temperature this feature is brought out clearly. Whereas in the ordinary case of paratyphoid the tracing of the pulse is well below that of the temperature, in more severe conditions the pulse tracing rises, first intermingling with the temperature record and then rising more and more above it. Inspection of Chart II illustrates this point well. The pulse tracing at first blended with but soon rose above the temperature tracing, and was from the first prophetic of evil, keeping at a high rate while the temperature was intermitting. The same point is well illustrated by Case 1; the patient was toxic and had broncho-pneumonia from infection by paratyphoid A. On the seventeenth day there was improvement both in pulse and temperature. On the twentieth day the temperature rose moderately, but the pulse tracing rose above it, and on the twenty-fourth day perforation occurred.

This tachycardia during the active stage of the disease only holds its significance so long as the temperature is above 100° F. It must be carefully distinguished from the tachycardia of convalescence, which has features of its own.

The pulse was soft and in six of the seventeen cases dicrotic. The apex beat in paratyphoid is not infrequently difficult to palpate, and in such cases with the polygraph a cardiogram can with difficulty be obtained. This is in keeping with the flabby and pale condition of the cardiac muscle sometimes found. Displacement outwards of the apex beat was not a marked feature, even when the heart was failing. Endocarditis was not once recorded.

The blood pressure varies. The highest recorded systolic pressure in this series was 130. It is more commonly 115–110, or even lower. The difference in reading between the diastolic and systolic pressure seemed small.

In three cases special study was made of the circulation by Captain Marris.
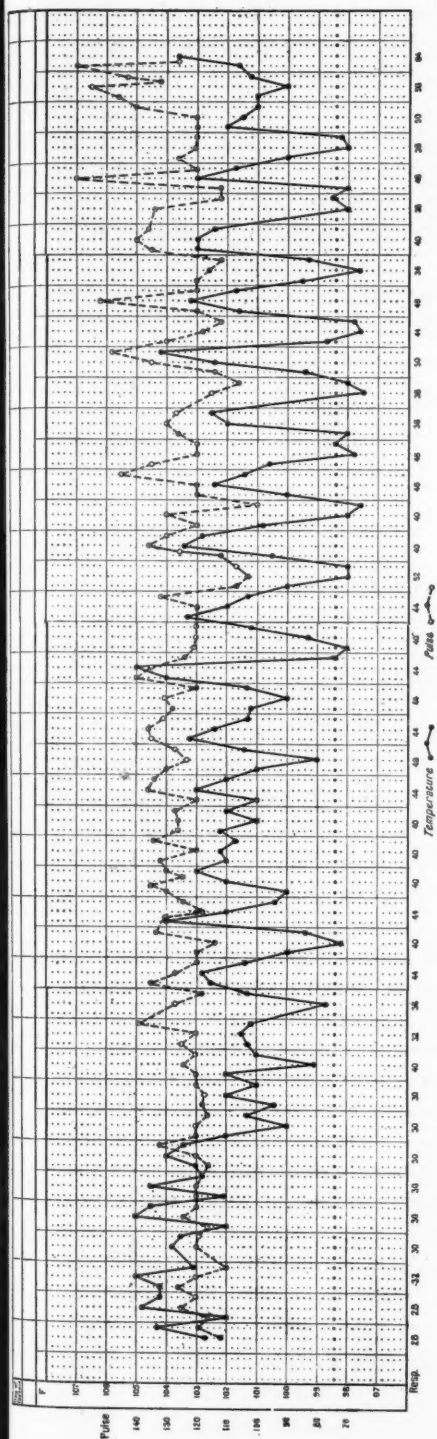
CHART III.
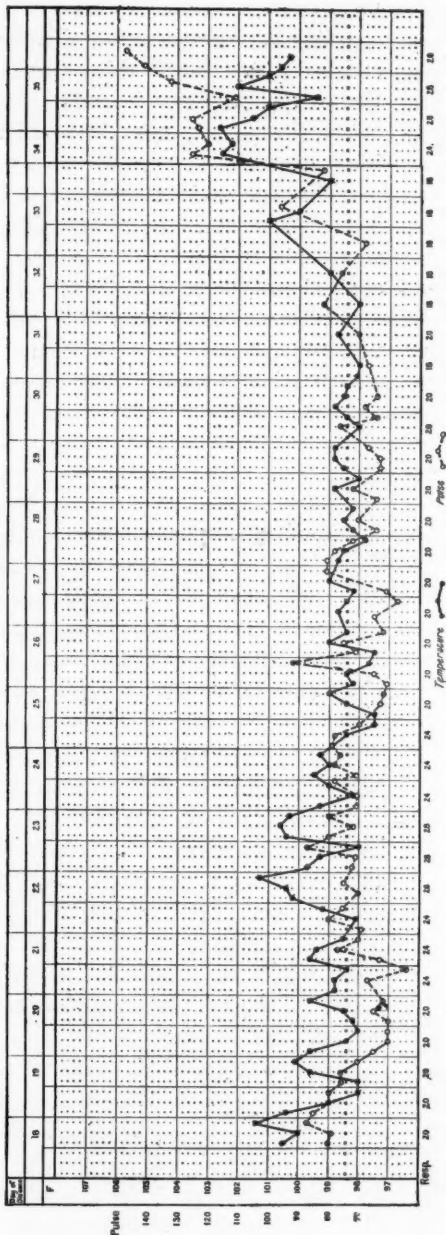
Case 15.   Pulse 90–125 dicrotic.   Blood pressure 110–115 throughout.
A few days before death ventricular extra-systoles occurred.   This was a very
toxic case which developed a suppurative parotitis, probably due to a very dry
mouth and pharynx.

Case 9.   Pulse 120–130 dicrotic.   Blood pressure 120–130.   Vessels thick
and tortuous.   On the thirty-fourth day showed heart-block as well as alterna-
tion of pulse.   Periodic respiration during the three days preceding death.
Heart, though large and fatty, did not show enlargement to percussion during
life.

Case 16.   Pulse mounted from average of 100 to 120 and 130, and reached
168 before death.   It was dicrotic throughout.   The systolic blood pressure
was 95, dropping to 75 twenty-four hours before death with a diastolic of
approximately 50.   Heart *post mortem* was pale, flabby, and rather small.

When the condition of the patient was grave $\frac{1}{100}$ gr. strophanthin intra-
venously reduced the pulse from 168 to 145 in fourteen minutes, and later
a second dose reduced it from 145 to 125.

The Spleen.

In eight cases the spleen was found enlarged *post mortem*; in six of these
the enlargement had been detected during life, and in two it had not.   In one
case (No. 15) the spleen was half the normal size.

In the two following cases there were abscesses of the spleen.

Case 14, *Chart III.*   Admitted on the eighteenth day of disease com-
plaining of pains all over, which were worse on left side of the chest and on deep
breathing; abdomen not distended; spleen not palpable, but its region was
tender; the pulse was slow, fever slight, and the general aspect was one of mild
infection.   On the twenty-second day there was a sharp pain at the left base,
increased by breathing, but no physical signs except weakness of breath sounds.
The pain passed and the general condition improved until suddenly, on the
thirty-fourth day, the patient vomited, the temperature rose to 102·6° and the
pulse to 128.   Twelve hours later there were pain and rigidity on the left side
of the abdomen, and the general condition, as shown by cyanosis and weak rapid
pulse, was worse.   On the thirty-fifth day there was falling temperature with
rising pulse, and hiccough supervened.   On the thirty-sixth day death
ensued.

Post mortem there were no macroscopic lesions in the intestine.   The
spleen (Plate 7), however, presented the following features.   It was considerably
enlarged and dark red in colour.   The upper pole was adherent to the stomach,
and the lower pole was fixed to the colon.   The lower pole was converted into
an abscess cavity of the size of a hen's egg and contained thick curdy pus.
Half an inch above and anterior to this abscess the surface of the spleen was
mottled white and purple, and beneath this area another small abscess was

found.   Towards the hilum there was a third abscess cavity an inch in diameter and of irregular outline.   The remaining pulp was congested and friable.

There was no perforation and no signs of peritonitis, and it is not quite clear why this patient died and so quickly.

Bac. paratyphoid B was obtained from the splenic abscess and pulp, and from the bile.

In life, cultures from blood, stools, and urine were negative.   Agglutination was positive with paratyphoid B.

The full table was as follows :

	Dilutions	50	100	250	500	1,000	2,500
19th day	Typhosus	+	+	+	—	—	—
	Para. A	—	—	—	—	—	—
	Para. B	+	+	+	+	—	—
24th day	Typhosus	+	+	+	+	+	—
	Para. A	—	—	—	—	—	—
	Para. B	+	+	—	—	—	—

This case is an interesting example of paratyphoid without the usual localization in the intestine.

Case 7, Chart IV.   Admitted on the ninth day ill, but only slightly toxic, with a characteristic tongue, a flat abdomen, diarrhoea and typical stools, but no spots and no splenic enlargement.   Except for a persistence of the diarrhoea, progress was continuous and satisfactory until the twenty-third day, when perforation of an ulcer in the sigmoid occurred.   There was a sudden onset of acute abdominal pain.   Two hours later the abdomen was distended, motionless, and diffusely tender, and the liver dullness was absent.   Operation five hours after the onset disclosed gas and faeces in the peritoneal cavity and three perforations in one necrotic ulcer in the sigmoid.   The ulcer was sutured. Death occurred thirty-six hours later.   It will be observed that perforation took place after an afebrile interval of six days.   The patient had been cautiously fed.

At the autopsy there were six clean, healing ulcers of the ileum near the caecum.   The large gut was thickly studded from caecum to rectum with punched-out ulcers, several of which were near perforation, besides the one which had given in the sigmoid.

The spleen contained two abscesses, each the size of a pigeon's egg.   The bases of the lungs were engorged.   Other organs called for no comment.

The bacteriological findings were as follows : blood culture was negative on the tenth day ; three stools were negative on the tenth, eleventh, and twelfth days ; the urine was negative on the tenth day, but positive on the sixteenth day.

Agglutinations were :

10th day	Typhosus	+	1 in 250
	Para. A	—	
	Para. B	+	1 in 50
14th day	Typhosus	+	1 in 200
	Para. A	—	
	Para. B	+	1 in 500

Post mortem both the bile and the spleen gave positive cultures of para-typhoid B.

The Intestines.

The small gut. In one case of paratyphoid A infection (No. 1) the ulcera-tion of Peyer's patches was very marked, whilst in the other (No. 2) there were obvious signs of the healing of recent ulcers in the intestine when the patient died from a subsequent typhoid infection. In twelve out of the fourteen paratyphoid B infections the small intestine was affected to a varying extent. Usually the Peyer's patches were deeply ulcerated, and the solitary lymphoid nodules were raised and varied in size from pinheads to large peas. The lower two feet of the ileum were the constant seat of the disease, and the neighbour-hood of the ileo-caecal valve was the area the most intensely affected. The floor of the ulcers was constituted by the muscular coat or the peritoneum, and the edges of the ulcers were usually undermined and in all cases thickened (Plate 8).

In two cases the small gut showed no lesions. One of them (No. 14) has been already referred to. In the other (No. 9) the large intestine was extensively ulcerated from the caecum to the pelvic colon. In a third case (No. 13), to be referred to later, there was no ulceration though Peyer's patches were raised (Plate 9).

Large intestine. Judging from this series of cases the disease falls with more force on the large intestine in paratyphoid than in typhoid. This is shown by the frequency and extent of the ulceration in the caecum, appendix, and colon. Thus in ten instances of paratyphoid B infection the large intestine from the caecum to the pelvic colon was involved, the ulceration being most marked in the caecum and the colon as far as the splenic flexure. In the milder examples the lymphoid nodules were raised, hyperaemic, and umbilicated, whereas in the severer forms there were ulcers of varying sizes and depths. A characteristic condition is shown in Plate 10, where the large bowel is riddled by small ulcers, some of which have coalesced. Notwithstanding the marked distribution of ulcers in the large intestine, it is noteworthy that there were no clinical manifestations especially suggestive of it. Moreover, in typhoid the large bowel is more often affected than is commonly supposed. The condition of the large intestine is not mentioned in two post-mortem records, and in the remaining two cases (Nos. 13 and 14) of paratyphoid B infection, in which neither the large nor the small intestine was ulcerated, there were abscesses in the liver and the spleen respectively.

Appendix. The appendix was a focus of mischief causing peritonitis in three cases. In two of these (Nos. 6 and 13), in which paratyphoid B was the cause, it was acutely inflamed. In No. 6 there was gangrene of the appendix, at the base of which there was a perforated ulcer. In the other case (No. 13)

CHART IX

CHART IV
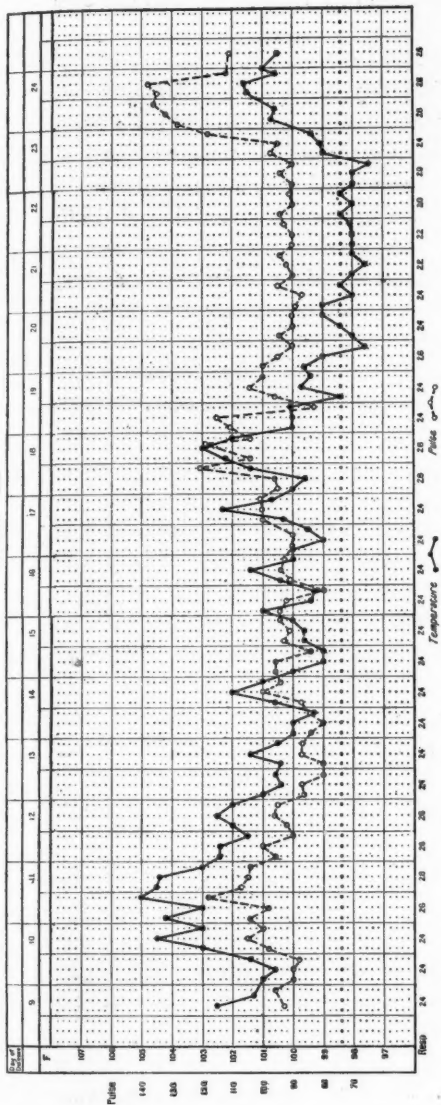
CHART V
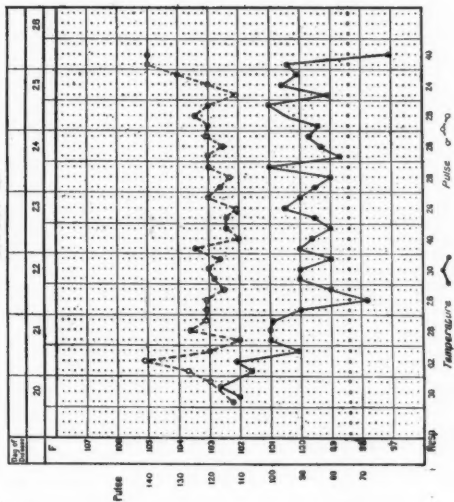
the tip of the appendix was intensely inflamed, general peritonitis and portal pyaemia had followed, and paratyphoid B was isolated from the pus both in the right iliac fossa and the liver.

The appendix was the seat of the perforation of a typhoid ulcer in one case of paratyphoid A.

These three cases are worthy of more detailed description.

Case 6, *Chart V.*　Admitted on twentieth day, drowsy, flushed, and toxic; abdomen slightly distended and painful; pulse rapid (110–120) and soft; heart and lungs showed no abnormal signs.　On the twenty-fifth day more abdominal pain with repeated vomiting, but the abdomen moved and was not distended. The vomiting consisted of bile and, later, of coffee grounds material, and death ensued on the twenty-sixth day.

At the autopsy the peritoneal cavity contained thin, purulent fluid, and its surface was injected everywhere.　The appendix was gangrenous in its proximal two-thirds and its mesentery also.　There was severe and deep ulceration for five feet above the ileo-caecal valve and affecting the solitary follicles rather than Peyer's patches.　Several ulcers were down to the peritoneal coat.　Mesenteric glands were of the typical chocolate colour.

The blood in life and the bile after death both gave a positive culture of paratyphoid B.

Case 13, *Chart VI.*　Admitted on the eleventh day, jaundiced and looking ill; the tongue was suggestive; the abdomen tumid and tender, especially over the gall-bladder; neither liver nor spleen was felt; there were a few spots. Pulse throughout indicated a severe infection.　Bowels were constipated, and the motions contained bile.　Patient became increasingly toxic, and abdominal tenderness became more marked.　On the twenty-sixth day a tumour was felt in the right lower quadrant of the abdomen and at operation pus was found, apparently connected with the appendix, and was freely drained.　There was only a transitory improvement after the operation.　The jaundice deepened, wasting and weakness increased, and death occurred on the fifty-seventh day.

At the autopsy there was diffuse peritonitis due to a gangrenous appendix bound down in an abscess cavity in the pelvis.　The liver was enlarged, and contained multiple abscesses.　A liver abscess had penetrated the right diaphragm and produced an abscess in the lower lobe of the right lung and an empyema at the base of the right pleura.　Peyer's patches were prominent, but there was no definite ulceration in small or large intestine.

The bacteriological findings were :

Blood culture negative on twelfth day.　Stool and urine cultures negative.

Agglutinations with all three organisms were negative in all dilutions from 1 in 50 to 1 in 2,500 on two separate occasions.

Pus from the abscess showed positive culture of paratyphoid B and so did the bile.

This case is remarkable in many ways.　Jaundice was a feature.　The

CHART VI
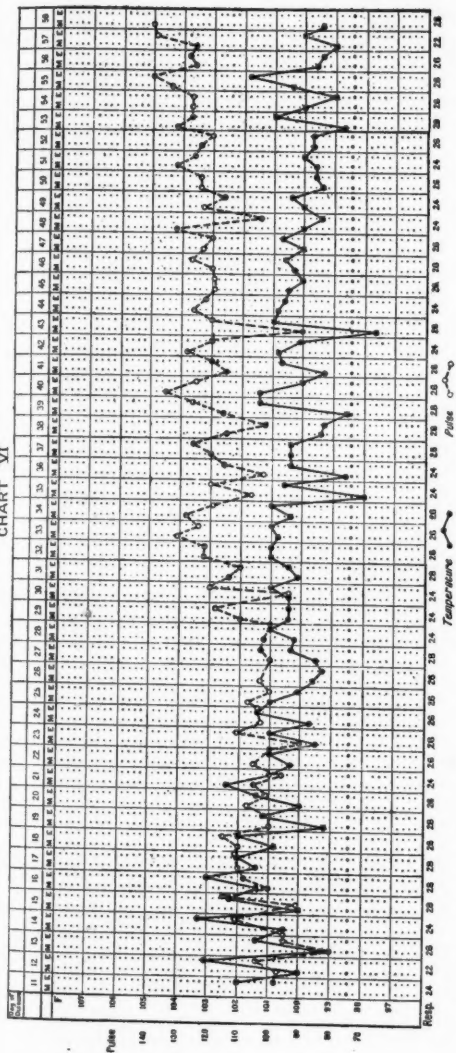
CHART VII
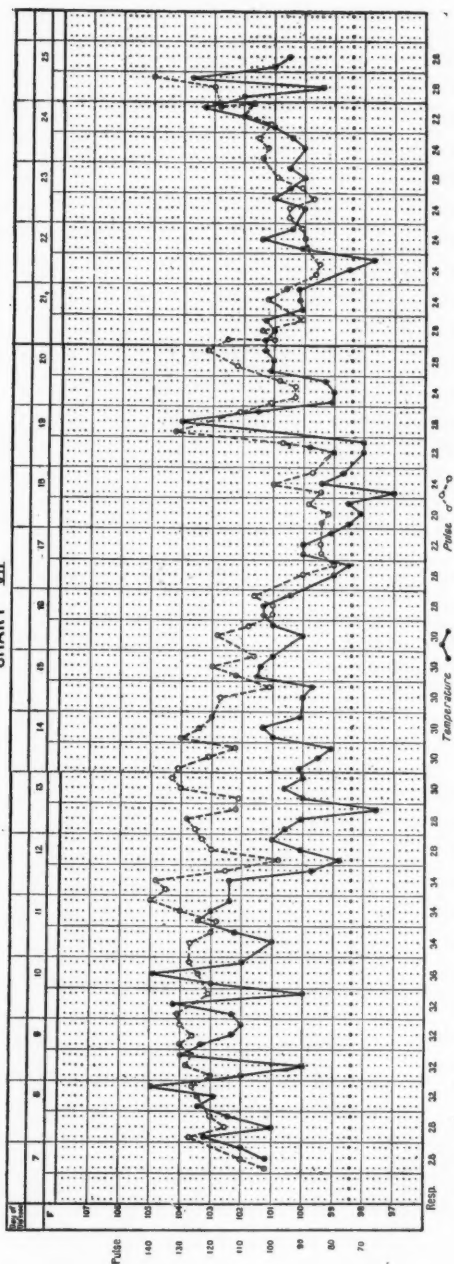
brunt of the disease had fallen on the appendix, and manifestations in the rest of the intestine were ill-defined. There was no acute perforation, but a secondary portal pyaemia and abscesses in the liver and lung. The blood, urine, and stool cultures and agglutinations were negative, supporting the view that negative bacteriological results are not so certain a guide as positive ones. These negative results are curious in the light of the fact that the pus from the liver and the bile gave positive cultures of paratyphoid B. An alternative explanation suggests itself, viz. that an acute appendicitis supervened at the end of a mild attack of paratyphoid fever, that the portal pyaemia was the result of the appendicitis, and that the liver abscesses were subsequently infected by paratyphoid from the biliary passages. In support of this view there was a history of two attacks of severe abdominal pain during the preceding twelve months.

Case 1, *Chart VII* is an example of paratyphoid A ending fatally from a perforation of an ulcer in the appendix. The onset was gradual, with malaise, fever, and diarrhoea. The patient was admitted on the seventh day, ill and toxic, pulse 110–120, tongue typical, abdomen not distended, spleen not enlarged, a few spots, and signs of bronchitis. On the ninth day spots were profuse, and broncho-pneumonia had supervened, and the general condition was worse, but there was no distension. On the sixteenth day some improvement was apparent, but on the nineteenth day there was a rigor and further infection. On the twenty-first day there was improvement in the lungs, pulse, and temperature. On the twenty-third day there were symptoms of peritonitis, but no pain or tenderness, and the clinical picture did not resemble that of an ordinary ruptured appendix. Death occurred on the twenty-fifth day. Blood culture on the seventh day showed paratyphoid A. The complete bacteriological findings are to be found in Table I.

Autopsy—general peritonitis. Some thin discoloured pus in the pelvis. The appendix pointed downwards and in its proximal third there was a perforation caused by a paratyphoid ulcer, above and below which the tissues were apparently normal (Plate 11). Peyer's patches were ulcerated above the ileo-caecal valve and in the caecum the follicles were also slightly ulcerated. The lungs showed broncho-pneumonia.

There were thus five cases of peritonitis, two caused by inflamed appendices, two by acute perforations, and in one the cause was undiscovered, though it was thought to be a perforation and was operated on for such. Of the perforations, one was situated in the appendix and the other in the sigmoid.

Haemorrhage contributed materially to the death of four patients (Nos. 8, 9, 15, and 16). In one of these (No. 8) the death occurred on the fourth day in hospital, and on the twentieth day of the disease, from severe and repeated bleeding. Two died on the thirty-eighth and thirty-ninth days of the disease respectively, and one not earlier than the thirty-fifth day. All four cases were toxic. In three of them both large and small intestines were ulcerated, and

in a fourth the ulceration was confined to the large gut.   In no instance could any focal origin of bleeding be confidently determined.

There were two cases of mixed infection, viz. (*a*) paratyphoid B with cerebro-spinal meningitis, the organism of the former being isolated from the blood and stool and that of the latter from the cerebro-spinal fluid ; (*b*) the other (2) was specially interesting for the following reasons :

(*a*) The patient had a double infection by the Bac. paratyphosus A and the Bac. typhosus.

(*b*) He had thrombosis of the left femoral and left external iliac veins.

(*c*) Four relapses occurred during the course.

(*d*) In the last relapse he had pulmonary infarction, and death was due to the subsequent severe lung affection on the 127th day from the onset.

A full account of the bacteriological examinations is given in Table I (Case 2).   The following points are noteworthy : The patient had had no protective inoculations.   Admitted on the twelfth day of the illness, the patient appeared to be typical of a rather' severe enteric group infection, and his blood gave a pure culture of Bac. paratyphosus A.   The serum on this day and on the eighteenth day strongly agglutinated the stock paratyphoid A bacillus, and gave no reaction with Bac. typhosus or Bac. paratyphosus B.   By the twenty-second day the patient was obviously improving, and during this time he had had a swinging temperature (rather characteristic of paratyphoid A infection) from 99° to 102°.   On the twenty-third day, however, the temperature range became steadier, remaining between 102° and 104° for five days.   On the twenty-fourth day the serum agglutinated Bac. typhosus as well as Bac. paratyphosus A.   It gave the same reaction on the twenty-ninth day, but the reaction with Bac. paratyphosus A had much diminished.   On the twenty-seventh day thrombosis of the left femoral vein was first noted.   The duration of this primary attack of fever lasted forty-eight days.

The patient had four relapses with four, twenty, sixteen, and ten days' pyrexia respectively.   During the second relapse the patient was given two injections of paratyphoid A vaccine without obvious effect.   In the middle of the third relapse a blood culture was negative.   At the post-mortem a pure culture of Bac. typhosus was grown from every viscus examined (gall-bladder, spleen, mesenteric gland, and thrombosed vein), thus proving the presence of a second infection.

The date of the second bacillary invasion is not quite clear.   The agglutination reactions suggest that it was before the twenty-fourth day, but not much before the eighteenth day ; also the temperature range altered on the twenty-third day.

Thus it would seem likely that when the patient came into hospital he had reached the twelfth day of a paratyphoid A attack and was in the midst of the incubation period of typhoid ; that for a while the two infections reigned together, and later the paratyphoid A disappeared, leaving the typhoid to reign alone.   The relapses were thus probably due to Bac. typhosus.

The causes of death may be summarized as follows :

Perforation	2 cases
Peritonitis from infected appendix	2 ,,
Haemorrhage	2 ,,
Haemorrhage and toxaemia	3 ,,
Toxaemia	4 ,,
Pneumonia	2 ,,
Splenic abscess	1 ,,

These represent a death-rate of rather over 4 per cent. for paratyphoid B and under 1 per cent. for paratyphoid A.

Complications.

Apart from perforation, haemorrhage, and pulmonary manifestations, these cases seem to point to a tendency to pus formation. Thus abscesses of the spleen were found twice (Nos. 7 and 14) ; round appendix twice (Nos. 6 and 13) ; in the liver once (No. 13), and of lung twice (Nos. 3 and 13) ; and empyema occurred in connexion with one of the lung abscesses.

Beyond these there was one instance (No. 2) of left femoral thrombosis with pulmonary infarct and left pleural effusion.

No small part of the value of these records lies in the complete bacteriological observations, for which we are greatly indebted to Captain J. L. Wood and Captain W. H. Tytler.

Treatment.

Followed the usual lines. Two patients were treated with paratyphoid sensitized vaccine, one (No. 2) as above, and the other (No. 3) received 250 millions on the eighteenth, 375 millions on the nineteenth, and 500 millions on the twentieth day. Neither benefit nor the reverse apparently followed.

Laparotomy was performed on four of these cases, on two for peritonitis due to suppuration round the appendix (Nos. 6 and 13), and on two for perforation. In one of the latter (No. 10) the evidence at the onset was vague, and operation was not undertaken until twenty-four hours later, and even then the ulcer which caused the peritonitis was not found ; but in the other (No. 7) the abdomen was opened within five hours of the commencement of symptoms. The results in these two cases are in keeping with those for perforation generally at the hospital in which these cases occurred. So far there has been no recovery, and this notwithstanding that the external conditions give every chance for success in that the patients are constantly under the eyes of skilled observers and the surgery is in the hands of a skilled abdominal operator, Major Davies-Colley.

It is the internal conditions which are so unfavourable. For one ulcer which is through there may be several which are nearly so, and the reactive power, both local and general, is down to vanishing point. This was so, for

instance, in Case 7, in which there were several ulcers almost as bad as the one which had actually perforated.   It would seem that the only cases in which we can expect success are those in which some odd ulcer has gone deeper than its fellows and perforated the weak link in a chain which otherwise has some strength left; and it is these fortunate cases which fully justify resort to operation when perforation has been diagnosed, and provided sufficiently skilled surgical aid is available.

TABLE I. *Summary of Symptoms and Signs and*

No.	Protective Inoculations against Typhoid.	Onset.	Condition on Admission.	Tongue.	Pulse.	Rash.	Abdomen.	Spleen.
1.	+2	Gradual, with diarrhoea and great weakness. No headache. No epistaxis	8th day. Toxic, pinched, and cyanosed. T = 101°. P = 108. R = 28.	Furred and sticky	110-120. Not dicrotic.	8th day. A few spots on abdomen. 14th day. Profuse	Not distended or tender on admission	Never enlarged
2.	0	Headache, cough, abdominal pain, diarrhoea. No epistaxis	13th day. Drowsy and mentally weak. T = 102·8°. P = 108. R = 28.	Dry and furred	Small and compressible. Not dicrotic	13th day. A few spots on back. 20th day. A fresh crop.	Not distended or tender on admission	14th day. + (felt). And again during first relapse
3.	+2	History not obtained	8th day. Lethargic and toxic. Typical appearance of severe case. T = 103°. P = 110. R = 28.	Dry, brown fur. Shiny tip and edges	Big volume. Soft and dicrotic	No spots seen	Not distended. No tenderness	8th day. + (easily felt)
4.	+2	History could not be obtained	4th day. Seemed a mild case, but mentally peculiar, refusing to speak. T = 100°. P = 84. R = 24.	Dry, thickly furred. Edges clean	Big volume. Not dicrotic	Big, markedly raised spots (? Para. B)	Rather distended. Moved well and was not tender	4th day. + (just felt)
5.	+2	General weakness. Chilly. Abdominal pain. No epistaxis or headache	18th day. Appeared severe. Vomiting, abdominal pain and diarrhoea. T = 103°. P = 120. R = 32.	Thick fur	Low tension	21st day. Spots present	Soft, but distended and tender	+ (not felt)

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Clinical Course, with the Bacteriological Reports.

Lungs.	*Stools.*	*Course.*	*Bacteriological Reports.*
General bronchitis. Later severe	Typical loose brown. Some diarrhoea	12th day. Broncho-pneumonia 19th day. Rigor 23rd day. Peritoneal appearance. Abdomen quite flaccid 25th day. Died	*During life.* Blood culture, 7th day = Bac. Para. A Agglutination reactions not done *Post mortem*, 25th day. Culture from gall-bladder = Bac. Para. A
13th day. Bronchitis 114th day. Gradual increase in signs in left lung, with blood-spitting and acute pain in left side of chest	13th–27th days. Had slight diarrhoea. After this had constipation	23rd day. ?Fresh infection 28th day. Left femoral thrombosis 40th day. General condition good 53rd day. Relapse 87th day. Relapse 114th day. ?Infarct of left lung and relapse 121st day. Right heart dilated 128th day. Died	*During life.* Blood culture, 12th day = Bac. Para. A. Blood culture, 97th day (10th day of relapse) = neg. Agglutinations :— [1] 12th day, T = 0, A = 1/500, B = 0 18th day, T = 0, A = 1/500, B = 0 24th day, T = 1/250, A = 1/500, B = 0 29th day, T = 1/250, A = 1/50, B = 0 36th day, T = <1/50, A = <1/50, B = <1/50 *Post mortem*, 126th day. Cultures from gall-bladder, spleen, mesenteric gland, and from a thrombus in the left exterior iliac vein grew Bac. typhosus
8th day. Nil 15th day. Bronchitis 21st day. Broncho-pneumonia 23rd day. Dullness + over right base; ?empyema. Chest explored 27th day. Dullness at both bases	Loose, at times undigested. 1–2 per diem until two days before death, when severe diarrhoea started	Gradual involvement of both lungs 23rd day. Swinging temperature (97°–103°) from now onwards: ?rapidly advancing tubercular affection. Appearance not typhoidal. Patient was at times fairly bright. 3 doses of Para. B vaccine without appreciable effect 29th day. Died	*During life.* Blood culture, 8th day = Bac. Para. B. 23rd day, fluid from lung puncture sterile. No tubercle bacilli in sputum Agglutinations :— 8th day, T = 1/100, A = 0, B = 0 15th day, T = 1/250, A = 1/25, B = 1/500 Smear made from material obtained by lung puncture showed no bacilli *Post mortem*, 29th day. Cultures from gall-bladder and from lung grew Bac. Para. B
4th day. Nil. R = 24 6th day. R = 34 8th day. Crepitations and tubular breathing at right base and less so at left base	Loose brown. Not frequent	6th day. Definite turn for the worse, and case took on the aspect of noisy delirious lobar pneumonia 11th day. Died	*During life.* Blood culture, 7th day = Bac. Para. B Agglutinations :— 7th day, T = 1/250, A = 0, B = 1/100 11th day, T = 1/500, A = 0, B = 1/25 The patient's serum agglutinated strongly the bacillus isolated from his blood *Post mortem*, 11th day. Culture from gall bladder grew Bac. Para. B
18th day. Nil 21st day. Bronchitis	Diarrhoea throughout. 9–11 per diem	Increasing toxaemia 21st day. Died	*During life.* Blood culture, ?16th day = Bac. Para. B. Stool culture, ?16th day = Bac. Para. B Agglutinations :— T = 1/3,000, A = <1/100, B = 1/4,000 *Post mortem*, 21st day. Culture from gall-bladder grew Bac. Para. B. Culture from lung showed no organisms of enteric group

[1] These cases, with the exception of No. 16, were in this hospital before standard emulsions had come into general use. The various dilutions mentioned therefore cannot be compared. In most cases, however, the same emulsions were used for all the tests made on a particular case.

TABLE I

No.	Protective Inocula- tion against Typhoid.	Onset.	Condition on Admission.	Tongue.	Pulse.	Rash.	Abdomen.	Spleen.	
6.	+2	Diarrhoea, vomiting, ab- dominal pain, epistaxis	? 20th day. Typical of a severe case of enteric group infection. T = 102°. P = 112. R = 28.	Furred	112–120. Low tension	A few spots on abdomen	Tender and slightly dis- tended. 25th day. Not dis- tended	+ (felt)	? 2(N nc
7.	+1	Headache, back- ache, pain in abdomen and limbs. Shiver- ing, diarrhoea. No vomiting. No epistaxis	9th day. Toxic. T = 103°. P = 96. R = 24.	Dry, furred	Dicrotic. Very soft	No spots seen	9th day. Nil. 11th day. Elastic and slightly dis- tended	+ (not felt)	9th tis up
8.	+2	History could not be obtained	? 20th day. Toxic, deli- rious. Typical of a severe typhoid case. T = 101·8°. P = 112. R = 24.	Dry, brown. Shiny at tip. Typical	Dicrotic. Very soft	A few big spots	Fullness. No ten- derness	+ (not felt, but markedly enlarged to per- cussion)	Nil
9.	+2	Gradual. Ab- dominal pain. Three weeks diarrhoea. Epi- staxis on two occasions	19th day. Head- ache, abdo- minal pain and diarrhoea. Typical group infection, prob- ably Para. B. T = 103·8°. P = 76. R = 20.	Thick fur	Dicrotic.	Several rose spots of large para- typhoid type. 30th day. Spots very notice- able	Tumid. No ten- derness	+ (not felt). 28th day. (felt)	19th No th
10.	+2	General weak- ness, slight diarrhoea and abdominal pain. Severe headache. No epistaxis	9th day. Dusky with malar flush. Head- ache, mentally clear. Moder- ately severe and typical paratyphoid. T = 100·6°. P = 84. R = 20.	Dry, cracked, clean at edges and tip	Dicrotic. Good volume. Very soft	A few big, well- raised spots (? Para. B)	Not dis- tended. Nil ab- normal	9th day. Not en- larged. 12th day. + (felt)	No i lun

(*continued*).

Lungs.	Stools.	Course.	Bacteriological Reports.
?20th day. Nil. Never had abnormal signs	Diarrhoea throughout. 2-6 per diem	24th day. Toxic, but general condition seemed improved 25th day. Vomiting, abdominal pain, abdomen moved well and liver dullness normal 26th day. Died	*During life.* Blood culture, ?20th day = Bac. Para. B Agglutination reaction of serum not tested *Post mortem,* ?26th day. Culture from gallbladder grew Bac. Para. B
9th day. Bronchitis. This cleared up later	Typical. Diarrhoea after 11th day. 3-5 per diem	9th to 22nd days. Steady improvement to convalescence 20th day. Pea-soup stools 23rd day. Sudden abdominal pain, peritonitis, laparotomy 25th day. Died	*During life.* Blood culture, 10th day = neg. 3 stool cultures and one urine culture from 10th to 13th days = all neg. Urine culture, 15th day = Bac. Para. B Agglutinations :— 10th day, T = 1/250, A = 0, B = 1/50 15th day, T = 1/250, A = 0, B = 1/500 *Post mortem,* 25th day. Cultures from gallbladder and spleen grew Bac. Para. B Culture from lung showed no enteric group bacilli Smear from lung showed no Gram-negative bacilli
Nil	Typical greenish-brown. 1-2 per diem	?22nd day. Slough (?) passed ?23rd day. Haemorrhages, large and repeated ?24th day. Died suddenly	*During life.* Blood culture, ?20th day = Bac. Para. B. Cultures from stool and urine of same day also gave Bac. Para. B Agglutinations :— ?20th day, T = 1/320, A = 0, B = 1/540 *Post mortem,* ?24th day. Culture from gallbladder grew Bac. Para. B
19th day. Clear. No bronchitis throughout	Constipated, until 3 days before death	22nd to 33rd days. Increasing toxaemia 33rd day. Tender left side of abdomen, but no rigidity 34th to 36th days. Haemorrhages 38th day. Heart failing 39th day. Died	*During life.* Blood culture, 20th day = neg. Stool and urine cultures on 20th day also negative Agglutinations :— 20th day, T = 1/1,000, A = 0, B = 1/1,000 26th day, T = 1/20,000, A = 0, B = 1/20,000 35th day, T = 1/1,000, A = 0, B = 1/1,000 *Post mortem,* 39th day. Culture from gallbladder grew Bac. Para. B Cultures from spleen and lung were negative to enteric group
No involvement of lungs	1-2 per diem	12th day. Drowsy. Abdomen hollowed 13th day. Had had two doses of Para. B vaccine without obvious effect 14th day. Toxic. Abdominal pain 15th day. Pain and rigidity over lower abdomen, especially left iliac fossa. Vomited. ? Shut off perforation. ? Peritonitis without perforation 16th day. Laparotomy. No perforation found. General peritonitis 17th day. Died	*During life.* Blood culture, 9th day = Bac. Para. B. Stool culture, 11th day = Bac. Para. B Agglutinations :— 9th day, T 1/100, B = 1/100 *Post mortem,* 17th day. Culture from gallbladder grew Bac. Para. B. Cultures from the spleen and from a sub-peritoneal haemorrhage grew Bac. coli. A culture from a haemorrhagic area in lung grew staphylococci, but a smear from the lung showed Gram-negative bacilli

TABLE I

No.	Protective Inoculations against Typhoid.	Onset.	Condition on Admission.	Tongue.	Pulse.	Rash.	Abdomen.	Spleen.
11.	+1	History could not be obtained	10th day. Flushed, delirious, suggestive appearance. T = 103°. P = 124. R = 28.	Dry, furred, cracked, typical	Soft, but not dicrotic	Nil definite (had scabies)	Soft, tumid, tender	Notmade out to be enlarged
12.	?	History could not be obtained	5th day. Flushed, drowsy, lethargic. Very toxic. T = 103°. P = 100. R = 32.	Dry, brown, very typical	Full, but easily compressible	No spots seen	Distended. Tender in region of spleen	+ (not felt)
13.	0	Anorexia, constipation, abdominal pain. No diarrhoea, vomiting, or epistaxis. (Two attacks of severe abdominal pain in last 12 months)	11th day. Slightly jaundiced, looked ill. T = 102°. P = 98. R = 24.	Fairly moist. Furred, but clean at edges	Full volume, medium tension	A few suspicious spots	Tumid and tender over gallbladder. 13th day. Markedly distended	Not enlarged at first. 23rd day. + to percussion
14.	+1	Headache, pains in limbs, joints, and abdomen. Vomited. No diarrhoea	18th day. Quite clear mentally. Pains all over, especially in left side of chest on drawing a deep breath. T = 100°. P = 80. R = 20.	Rather dry, but quite clean. Not typical	Low tension	No spots seen	Not distended. Especially tender over splenic area	Notmade out enlarged

(continued).

Lungs.	Stools.	Course.	Bacteriological Reports.
Slight bronchitis at first. Later severely involved	Constipated throughout	12th day. Toxic. Lungs seemed choked at bases, but good percussion note 14th day. ? Aspiration pneumonia at both bases. Death	*During life.* Blood culture, 10th day = Bac. Para. B Agglutinations :— 10th day, T = 1/640, B = 1/120 *Post mortem,* 14th day. Cultures from gall-bladder, a mesenteric gland, and from the blood in one of big veins near heart all grew Bac. Para. B. A culture made from pus in lung showed no bacilli of the enteric group
5th day. Occasional râles 12th day. Much bronchitis	Fluid and typical. 3-8 per diem	7th day. More toxic 15th day. Haemorrhage (less than a pint) 16th day. Very severe. Nil in lungs to explain condition 18th day. Death	*During life.* Blood culture, 6th day = Bac. Para. B Agglutinations :— [2] 8th day, T = 1/120, B = 1/250 11th day, T = 1/25,000, B = 1/12,500 14th day, T = 1/250,000, B = 1/50,000 17th day, T = 1/125,000, B = 1/250,000 *Post mortem,* 18th day. Cultures from spleen and gall-bladder both grew Bac. Para. B. Culture from faeces grew ? Proteus
Little, if any, involvement of lungs	Alternate constipation and diarrhoea. Chiefly constipation	11th to 25th days. Constant abdominal pain, increasing distension and toxaemia 26th day. Mass felt in right iliac fossa. Abdomen soft and pulse better. Jaundice increasing. Laparotomy : shut-off abscess in appendix region opened and tubes inserted 34th day. Wound opened up and tubes reinserted 53rd to 58th days. Jaundice deepened and slowly went downhill 58th day. Death	*During life.* Blood culture, 12th day = neg. Three stool cultures and one urine culture during the 12th to 24th days were all negative Agglutinations :— 12th day, T = <1/50, A = <1/50, B = <1/50 24th day, T = <1/50, A = <1/50, B = <1/50 *Post mortem,* 58th day. Cultures from gall-bladder and from abscess in liver both grew Bac. Para. B. Culture from spleen showed no enteric group bacilli
No involvement of lungs	Decidedly constipated throughout	22nd day. Sharp pain in left lower chest 33rd day. Doing well. Uninterrupted progress 34th day. Severe vomiting and rise of temperature. Hollowed and flaccid abdomen. Later, severe pain in left upper abdomen with rigidity 35th day. Abdomen very retracted. Very weak. Hiccough 36th day. Died	*During life.* Blood culture, 16th day = neg. Agglutinations :— 16th day, T = 1/250, B = 1/500 24th day, T = 1/1,000, B = 1/100 *Post mortem,* 36th day. Cultures from gall-bladder, from spleen pulp, and from splenic abscess all grew Bac. Para. B. A culture made from blood within the heart was sterile. Serum from blood taken from heart agglutinated T = 1/500 and B = 1/500

[2] *Case No.* 12. Agglutination tests made by Dr. Inman with very dilute emulsions and heated at 55° C. This series is comparative. No information could be obtained about protective inoculation in this case. The agglutination curves suggest that he had been inoculated.

TABLE I

No.	Protective Inoculations against Typhoid.	Onset.	Condition on Admission.	Tongue.	Pulse.	Rash.	Abdomen.	Spleen.
15.	+2	History could not be obtained	? 2nd week. Lethargic, toxic, twitching of face muscles. Could not speak. T = 105°. P = 112. R = 24.	Very dry, also mouth and pharynx	Soft and dicrotic	A few typical ones. Later several crops	Not distended. Moved well	Not made out enlarged
16.	+2	Sudden, with diarrhoea, abdominal pain, and vomiting. No epistaxis	11th day. Flushed and toxic. T = 102·4°. P = 112. R = 24.	Furred, with red edges and tip	Big volume, but soft. Later markedly dicrotic	Several typical ones on chest	Not distended. Moved well	Not enlarged
17.	+1	Sudden. Vomiting, headache, and diarrhoea	11th day. Flushed and toxic. Vomiting continued. T = 102·4°. P = 112. R = 24.	Furred	Big volume, but soft	Several typical spots	Tumid. Suggestive typhoid feel	+ (not felt)
18.	?		Notes of this case have been lost. No post-mortem was performed					

(*continued*).

Lungs.	Stools.	Course.	Bacteriological Reports.
No involvement of lungs	Diarrhoea throughout. 4–7 per diem	Irregular pulse, and very lethargic. End of 3rd week (?). Parotitis incised —no pus. Later increasing toxaemia and haemorrhages. Difficulty in speaking and swallowing throughout. Died ?early in 5th week	*During life.* Blood culture, ?2nd week = Bac. Para. B. Stool culture, ?3rd week= Bac. Para. B. Three urine cultures and two stool cultures before this all negative. Agglutinations :— 2nd week, T=1/250, B=<1/50 End of 3rd week, T=1/10,000, B=1/5,000 Culture from parotid swelling showed no enteric group bacilli *Post mortem*, ?early in 5th week. Cultures from gall-bladder and spleen both grew Bac. Para. B
Bronchitis	Typical. Some diarrhoea	Advancing toxaemia, with very weak and irregular pulse (110–130) 32nd day. Severe haemorrhages 38th day. Died	*During life.* Blood culture, 17th day=Bac. Para. B. Stool culture on same day also grew Bac. Para. B Agglutinations :— 17th day, T = 1/80 (20 units), A and B < 1/50 23rd day, T=1/900 (230 units), B=1/5,500 (2,750 units) 30th day, T = 1/3,500 (895 units), B = 1/24,000 (12,000 units) *Post mortem*, 38th day. Cultures from gall-bladder and spleen both grew Bac. Para. B
Basal bronchitis	Typical. Diarrhoea throughout. 3–7 per diem	Gradually increasing distension and cardiac weakness 15th day. Severe haemorrhages 16th day. Death	*During life.* Blood cultures made on 10th and 12th days both grew Bac. Para. B. No agglutination tests were made *Post mortem*, 16th day. Culture from spleen grew Bac. Para. B
		The cerebral symptoms became prominent soon after admission and were the dominant feature throughout. Patient when admitted did not appear a severe case of paratyphoid fever	*During life.* A blood culture and a stool culture made in second (?) week of illness both grew Bac. Para. B. The cerebrospinal fluid showed microscopically the Meningococcus intra-cellularis, which organism was also obtained on culture

TABLE

No.	Peritoneum and Small Intestine.	Large Intestine and Appendix.	Mesenteric Glands.	The Spleen.
1.	*Peritoneum.* General peritonitis. Peyer's patches ulcerated in last 18″ of ileum	*Caecum.* Solitary follicles deeply ulcerated. *Appendix* 2½″ long : ulcer ¾″ × ¼″ had perforated through ulcer at its middle	Not mentioned	Not mentioned
2.	*Peritoneum.* Clean. Lower 4 feet, healed ulcers and some not quite healed	Not mentioned	Enlarged and pale	Large and pulpy. Two normal
3.	*Peritoneum.* Clean. Lower 6 feet of intestine ulcerated to submucosa and peritoneum	Not mentioned	Not mentioned	Not mentioned
4.	*Peritoneum.* Clean. Peyer's patches of ileum, marked ulceration and solitary follicles. Raised and central ulceration	Not mentioned	Not mentioned	Not mentioned
5.	*Peritoneum.* Clean. Superficial ulceration of Peyer's patches	Acute diffuse hyperaemia, prominent hyperaemic nodules. Ulceration of centre of lymphoid nodules	Not mentioned	Firm, not enlarged
6.	*Peritoneum.* General peritonitis in ileum, packed ulcers of Peyer's patches :— floor of ulcers—peritoneum	*Caecum.* Many ulcers and small ulcer at base of appendix. *Appendix* gangrenous throughout length	Enlarged and chocolate coloured	1½ normal, friable
7.	*Peritoneum.* General peritonitis. Six small healing ulcers in last foot	Intense hyperaemia and ulceration from caecum to pelvic colon. Perforation of ulcer at sigmoid flexure	Enlarged and some contained pus	Abscess at each pole
8.	*Peritoneum.* Clean. In ileum Peyer's patches swollen. Solitary follicles prominent and ulcerated	*Caecum.* Many small rounded ulcers. Solitary follicles of whole large intestine ulcerated	Congested	1½ normal, firm
9.	*Peritoneum.* Recent peritonitis in left flank. No evidence of ulceration of small intestine	Large and small, clean, but ulcers from caecum to pelvic colon	Slightly enlarged. Not typical	2½ normal, friable
10.	*Peritoneum.* General peritonitis. Semi-gangrenous ileum and submucous haemorrhages	*Caecum.* Early ulceration	Not mentioned	Not mentioned
11.	*Peritoneum.* Clean. Lower 2½ feet of ileum, marked ulceration of Peyer's patches, especially at ileocaecal valve	*Caecum* to splenic flexure profusely peppered with small punched out ulcers	Enlarged, hard and typical	1¼ normal, 'red septic spleen'

II.

The Liver.	The Kidneys.	The Heart.	Lungs and Pleura.	Summary.
Not mentioned	Cloudy swelling	Normal	Congested and broncho - pneumonia in places	Paratyphoid A ulceration of small intestine and appendix. Perforation of paratyphoid ulcer of appendix. General peritonitis
Mottled and pale	Nil	Flabby and dilated	Left pleural effusion and consolidation of left lower lobe	1st attack—paratyphoid A 2nd attack—typhoid
Not mentioned	Cloudy swelling	Nil	Acute gangrenous pneumonia (see text)	Paratyphoid B pneumonia
Not mentioned	Nil	Nil	Right lower lobe, red-grey pneumonic consolidation	Paratyphoid B ulceration of small intestine. Acute pneumonia
Congested	Cloudy swelling	Nil	Lungs congested	Paratyphoid ulceration of small and large intestine. Heart failure
Congested	Cloudy swelling	Nil	Lungs congested	Paratyphoid ulceration of small intestine. Ulcer at base of appendix gangrenous. Appendicitis
Normal. Pus in gall-bladder	Cloudy swelling	Toxic	Hypostatic congestion	Paratyphoid B ulceration of large intestine. Perforation. Pyaemia. Laparotomy
Normal	Normal	Normal	Normal	Paratyphoid ulceration of small and large intestine. Haemorrhages
Large and fatty. Bile turbid	Fatty	Fatty	Bronchiolitis	Paratyphoid B ulceration of large intestine. Haemorrhages
Not mentioned	Cloudy swelling	Normal	Broncho-pneumonia	Paratyphoid B ulceration of ileum and caecum. ? Perforation. General peritonitis
Liver and gall-bladder normal	Normal	Normal	Early broncho-pneumonia	Paratyphoid B ulceration of small and large intestine

TABLE II

No.	Peritoneum and Small Intestine.	Large Intestine and Appendix.	Mesenteric Glands.	The Spleen.
12.	Whole of ileum packed with large ulcers: sloughs recently separated	*Caecum* to rectum mucous membrane thickened	Swollen, soft and haemorrhagic	Firm, slightly enlarged
13.	*Peritoneum.* General peritonitis. Prominent Peyer's patches. No ulceration	*Appendix* long and the last $\frac{1}{2}''$ was gangrenous	Not mentioned	$2\frac{1}{2}$ normal, not friable
14.	*Peritoneum.* Clean. No obvious macroscopic lesion in small intestine. Microscope showed 'marked hyperaemia'	Nil	Hyperaemic	Large abscess in lower pole, two other small abscesses (see text)
15.	*Peritoneum.* Clean. Last 15″ of ileum, ulceration of Peyer's patches, severe at ileo-caecal valve	*Caecum.* Markedly ulcerated and extended to splenic flexure in lesser degree	Typical	Half the normal size
16.	*Peritoneum.* Clean. Diffuse superficial ulceration in lower 12″ of ileum. No relation to Peyer's patches	*Caecum* to rectum, small ulcers of solitary follicles and numerous large flat ulcers, whose floor was peritoneum	Not mentioned	Normal
17.	*Peritoneum.* Clean. Very extensive and severe ulceration			

(*continued*).

The Liver.	The Kidneys.	The Heart.	Lungs and Pleura.	Summary.
Gall-bladder distended with turbid bile	Cloudy swelling	Normal	Small patch of broncho - pneumonia at base of right lower lobe	Paratyphoid B ulceration of small and large intestine
Liver enlarged and riddled with small abscesses. Gall - bladder thick, wall not enlarged. Bile clear	Not mentioned	Not mentioned	Liver abscess had penetrated right diaphragm and caused empyema and abscess in the right lower lobe of the lung	Paratyphoid B hyperaemia of small intestine. Gangrenous appendicitis. General peritonitis. Portal pyaemia
Liver normal. Gall-bladder was distended	Soft and pale	Pale and flabby	Congested	Paratyphoid B infection of small intestine. Pyaemia. Abscesses of spleen
Not mentioned	Pale	Nil	Not mentioned. Paralysis of vocal cords	Paratyphoid B ulceration of small and large intestine. Haemorrhages
Large and fatty. Gall-bladder was distended	Nil	Small and flabby	Congested. Adhesions both sides of chest, dense and universal in right side	Paratyphoid B ulceration of small and large intestine. Repeated haemorrhages

DESCRIPTION OF PLATES.

PLATE 6.   Section of left lung.   The anterior portion of the upper lobe is congested, though aerated ; the posterior portion is consolidated, and there are two abscess cavities in the centre of areas of consolidation.

The whole of the lower lobe is occupied by broncho-pneumonic areas of consolidation, which in many places have broken down into abscess cavities. At the base of the lung a small abscess appears through the pleura.

PLATE 7.   The spleen shows a large abscess cavity at its lower pole, and along the anterior margin a small cavity has been opened.   Between these two cavities the spleen is mottled yellow and blue-grey, and indicates an underlying third abscess.   The wall of the lower abscess is adherent to the colon.

PLATE 8.   A lower portion of the ileum shows numerous ulcers, from which the sloughs have completely separated.

PLATE 9.   A Peyer's patch in the ileum, showing hyperaemia and early necrosis.

PLATE 10.   The ileum and caecum.   The ulcers in the ileum are deep, and the sloughs have in part separated.   The caecum is riddled by small ulcers, some of which have coalesced.

PLATE 11.   There is an ulcer of the appendix which has a large perforation ; the appendicular tissue around the ulcer was apparently healthy.

NEPHRITIS IN THE BRITISH TROOPS IN FLANDERS

A PRELIMINARY NOTE

By JOHN ROSE BRADFORD

DURING the earlier months of the campaign the number of cases of nephritis seen in the base hospitals was remarkably small, and in a group of such hospitals under my observation, where there were several thousand beds, I only saw, at this period, a few isolated cases of no great clinical interest. These were principally cases of chronic renal disease in men who had rejoined the army from the reserve, and where, under the stress of the campaign, the chronic malady had progressed more rapidly than usual, or where recrudescence of an old renal lesion occurred. These cases presented obvious physical signs of cardio-vascular changes such as high tension and arterial degeneration, and often other physical signs of chronic renal disease, e. g. the anaemia and such retinal changes as albuminuric retinitis. One of the most striking features of the medical cases admitted to hospital in the autumn and winter of 1914 was the rarity of renal dropsy. During this period, however, other maladies commonly reputed to be due to, or associated with, exposure to inclement weather were by no means rare. Thus, bronchitis and other pulmonary affections were prevalent, and there were also numerous cases of enteritis and colitis Further, during the wet and cold winter months, very large numbers of men were admitted with the so-called 'trench foot' resulting from exposure to cold and wet in the trenches. Even during this period, when the climatic conditions were very unfavourable owing to long-continued cold rain, and the hardships suffered by the troops were considerable, there was, so far as my experience went, no considerable number of cases of nephritis accompanied by obvious renal dropsy. Speaking generally, it may be said that the cases of nephritis were few in number until the months of March and April 1915. In these two months far more cases were admitted to hospital than the total admissions for the whole period of the war up to that date. The April admissions were greater in number than those of March, and the April admissions alone were not far short of the total admissions for the whole duration of the War to April. Further, if only the admissions from the troops that had been at the front since the commencement of the war were taken into account, the same conclusion is arrived at—the incidence of the disease

in March and April in these divisions is in marked excess to what obtained in the same divisions in the earlier months. Hence it is quite certain that the increase in the number of cases of nephritis was not due merely to the increase in the numbers of the British troops in the field in the later months, as compared with the numbers in the earlier months. It is impossible for several reasons to give the actual numbers in this preliminary communication, but not only in the early spring but also in the summer the increase in the nephritis cases was far greater relatively than the increase in the number of the troops in the field. Further, emphasis must be laid on the fact that not only did a great increase in the number of cases occur in the spring, i. e. in March and April, as compared with the earlier months, but the cases were also of a different type. Cases were now seen in large numbers with typical renal dropsy in so far as its distribution was concerned, and, as mentioned above, dropsical cases had been quite rare up to that time.

It may therefore be said that this outbreak of nephritis occurred in the spring of 1915, especially in March and April; the number of cases admitted increased still further in later months, and the occurrence of these cases has persisted until the present time with some fluctuations. The incidence was especially high in the summer months of 1915, but owing to increases in the strength of the forces in the field it is not possible at present to speak with certainty as to the actual case incidence. Again, during the later months more attention has been directed to the occurrence of the malady, more hospitals and further facilities for examination both at the front and at the bases have been provided, and hence the disease is doubtless more often recognized, especially in its slighter forms, owing to more thorough examination of cases of illness.

A special case-sheet was drawn up and issued, and all cases diagnosed as 'nephritis' were entered on such sheets, and the present preliminary paper is the result of a study of these case-sheets dealing with 1,455 cases under treatment at various periods since the outbreak in all the base hospitals of the Expeditionary Force in France. Further, at one of the bases all the cases of nephritis were segregated in one hospital, and these cases were seen repeatedly by me, and I also saw large numbers of cases in hospitals at other bases, so that in addition to the study of the case-sheets I have seen clinically some hundreds of cases. It is not possible to make such detailed and thorough examination of the cases in the hospitals with the forces in France, as is possible in the base hospitals in England, but some few points of clinical interest have emerged in the work here and form the substance of this communication. It is hoped that a more detailed analysis of the cases may be made later. When the early cases were first observed, two prominent symptoms attracted notice, the occurrence of oedema and the presence of dyspnoea. Often the soldier stated that the onset of the dropsy was quite sudden, absent on one day and very markedly present the next, and attracting the attention of his fellows. Not uncommonly the first sign of illness was the presence of dyspnoea, and, so far as my observations went, many men complained especially of nocturnal dyspnoea. This was quite a marked

feature of the onset and sometimes it persisted in a lesser degree for a few days. Others complained of dyspnoea on exertion, e. g. on the march. Objective dyspnoea was not however, a very marked feature of the majority of the cases clinically, when the patients came under observation in base hospitals—always several days after the onset of the illness. In some of the earlier observations, although albuminuria was present, casts were said to be absent, and this at one time gave rise to doubts in the minds of some observers as to the real nature of the dropsy. More extended observation has shown, however, that casts are very frequently present, and it is probable for several reasons that the percentage of cases in which the urine contains casts is really much greater than appears at first sight. In a series of 1,455 cases, casts were present in 794 cases, they were stated to be absent in 507 cases, and were not looked for in 154 cases.

The present paper will deal only with a series of 571 cases where casts were found to be present, although many of the statements made would apply to cases where casts were absent. I have thought it better not to include such cases, as doubts might be raised as to the accuracy of the diagnosis of nephritis in such instances. In the great majority of the 571 cases the casts were of the hyaline and granular varieties. In some, however, hyaline casts only are noted. In a considerable number, epithelial casts are also recorded as present. In most cases where casts were present they were readily found, and it was not infrequent for them to be present in abundance—this was especially the case with granular and hyaline casts. Blood corpuscles were also frequently found, but definite blood casts are not often recorded. White blood-cells are of course frequently found. In some instances, especially if the case is seen early, the urine is definitely smoky, and in others, but not in many, it may contain a large quantity of blood, so as to be obviously red to the eye. The latter condition, I would say from my own observations, is exceptional. Such cases present a rather different clinical picture to the general run of cases, in that with them dropsy is neither so frequent nor when present so marked a feature of the case.

Further, these haemorrhagic cases more frequently have pyrexia and resemble much more closely in their course infective nephritis dependent upon some microbic invasion. In some instances of this type of case the Bacillus coli communis has been recovered from the urine. In a few instances the haematuria and pyrexia have been intermittent and recurrent, producing a clinical picture closely resembling that seen in renal embolism; but these patients have not been suffering from any condition liable to cause embolism, and have presented no physical signs justifying such a diagnosis, and it seems more probable that the condition is due to some bacillary infection. These cases, however, are few in number and are quite different from the ordinary form of nephritis with which this communication deals, and where dropsy is really the dominant physical sign ; in these cases any considerable amount of blood in the urine is decidedly exceptional. The quantity of urine is notably decreased in all cases where dropsy is present, and especially so in the earlier stages of the malady whilst the dropsy is increasing. Quantities less than twenty ounces in the twenty-four hours are not

uncommon, and it is not unusual for a greater degree of suppression of the urinary flow to occur during short periods. In some cases complete suppression for periods of twelve to twenty-four hours has been observed, and in such cases it is usual for uraemic manifestations of considerable severity to be present. Even in these very severe cases it is most exceptional for death to take place. More often the suppression only lasts a few hours, and the urinary flow is fully re-established in 24–48 hours. Only three fatal cases have fallen under my direct observation in a series of several hundred cases of nephritis, and in all these suppression, together with uraemia, occurred, but none of these three fatal cases was really a case of simple nephritis. In one the condition was really the terminal stage of chronic Bright's disease which had run a more or less latent course and was only recognized in its last stage when uraemia had occurred. In the second case, which presented clinically the picture of an acute simple nephritis with dropsy, and where fatal uraemia ensued, post-mortem examination revealed the presence of congenitally malformed, atrophied, and hydronephritic kidneys with dilated ureters. Here the nephritis was implanted on kidneys already much impaired by a congenital lesion. In the third case it was found on post-mortem examination that one kidney only was present, the absence of the second was due here also to a congenital anomaly, and the one kidney present was deformed, either as the result of the atrophy of a portion of its substance as the result of an old infarct, or possibly congenitally. In this case also the nephritis had affected a kidney already impaired.

In all the other cases under my observation where suppression of varying degrees of severity developed, the patient recovered from any uraemic pheno-mena present and was ultimately well enough to be evacuated to England. It may be stated here that these three deaths are the only ones that occurred amongst the cases under my direct observation.

Dropsy occurs in the great majority of cases and is usually well marked, and, as mentioned above, it is, in a large proportion of cases, the initial pheno-menon that leads the soldier to seek medical advice. The dropsy may first attract attention by affecting the face, the patient giving the usual history of not being able to open his eyes in the morning, or not infrequently the dropsy is first noticed in the legs. Some of the patients complained greatly of the swelling of the abdomen, and anasarca of the abdominal wall was often well marked. Ascites, usually only of moderate degree, was present in a certain number of cases, but so far as my own observations went, it was not present in the bulk of the cases, and when present was never large in amount, and no case calling for paracentesis abdominis occurred. Much of the swelling of the abdomen com-plained of by the patients was really due to the oedema of the parietes. Oedema of the scrotum was not uncommon, and the well-known cushion of oedema over the sacrum and loins, so often seen in kidney disease, also occurred, but it was very exceptional for the dropsy to develop to the extent that is so often seen in nephritis in civil practice. Hydrothorax has occurred, but only in a very few instances, and pulmonary oedema with marked physical signs has been observed

not only in the cases with severe uraemic manifestations, but also in slighter degree in other cases with far less urgent symptoms of uraemia.

In all the above points, the dropsy seen in these cases of nephritis resembles very closely the nephritis as seen in civil practice. Thus it is most marked in the subcutaneous tissue and is prone to affect the face, scrotum, sacrum, and loins, and when marked to be accompanied with some collection of fluid in the great serous cavities, especially the peritoneum, and, finally, pulmonary oedema is not infrequent. There are, however, so far as my experience goes, certain points of difference. The most striking is the transitory duration of the dropsy; in some cases it might more properly be described as evanescent, as it may last only some two or three days. In a very large proportion of the cases, it does not persist for more than a week or ten days. There are some cases, but not a large number, where it is more persistent, lasting several weeks, but then there is nothing to distinguish such cases from those that every physician is familiar with in civil practice. The point of main clinical interest in the nephritis as seen in the hospitals in the field, is that large numbers of cases are seen where, notwithstanding the fact that the dropsy is quite marked in amount, it disappears rapidly with the most simple treatment. It is exceptional for it to be still present a fortnight after the onset, and it is only in a quite small proportion of cases that the dropsy resembles in its clinical course the form seen to accompany acute nephritis in civil practice.

It is remarkable, seeing the very large number of cases that have occurred, that the well-known facies of acute renal disease is so exceptional. The pale waxy or pasty swollen face so often seen in acute nephritis is, I would say, quite exceptional; this peculiarity may perhaps be associated with, or due to, the short duration of the dropsy. Further, although the dropsy is quite marked and obvious, I have seen no case where it was extreme in amount, and no case where any special methods of treatment, such as puncture, were necessary for its relief. This also is rather remarkable seeing the considerable number of cases that have come under observation. Lastly, no complications—such as secondary infections of the oedematous legs, gangrene, &c.—have come under my observation.

The dropsy accompanying this form of nephritis may therefore be said to be very frequent, the great majority of the cases suffering from it; it is marked in amount but never extreme. It is remarkable for its comparatively short duration and for not being accompanied with the marked anaemia and cachexia so usual in renal disease.

The albuminuria varied greatly in amount, especially as many of the observations were made on single casual specimens and not on a twenty-four hours' sample. Usually the amount present was very considerable, and in some cases the urine became solid on boiling. This was exceptional, and more usually an estimate formed by observing the amount of coagulum after boiling and subsequent standing of the urine would yield a result showing the presence of from $\frac{1}{4}$ to $\frac{2}{3}$ albumin by volume in the more severe cases. In a very consider-

able number of cases the amount was far less, and was described by the medical officer as a 'cloud', or a 'dense cloud'. The amount of albumin was sometimes small even when dropsy was present, but generally, when the albuminuria was slight, the dropsy was also slight or absent. Not infrequently the patient reached the base hospital when the dropsy had subsided and when the urinary flow was re-established, and these cases often presented a lesser degree of albuminuria, since the nephritis was really subsiding. Hence, it may be said that at the onset and during the height of the disease the albuminuria is considerable in amount and comparable to what is usually seen in the acute nephritis of civil practice. The albuminuria is much more persistent than the dropsy, and even in the cases where it disappears before the transference of the patient to England, it has usually lasted several weeks. The great bulk of the cases were, however, evacuated to England after the subsidence of the dropsy, and at a time when the urine still contained a variable quantity of albumin. It is not possible at the present time to speak with certainty as to the duration of the albuminuria, but the impression formed from the study of this large series of cases was that, in the great majority, the albuminuria was subsiding at the time of evacuation, and such reports as have as yet been received from England as to the subsequent history of these cases confirms this view, as the albumin is reported to have disappeared after a few weeks. It would seem, therefore, that in the majority of cases the nephritis subsides rapidly. Uraemic complications of varying degrees of severity are common, and sometimes they have been of great intensity. Many of the patients have a distinct urinous or ammoniacal odour, and in one case of only moderate severity the patient complained not only of headache, nausea, and dyspnoea, but also of a strong taste of ammonia in the mouth, this last symptom being the one that caused the most discomfort, and it was present within the first few days of illness, at a period when dropsy was present and the quantity of urine excreted daily amounted to thirty ounces. In this case the urine increased to fifty ounces with the subsidence of the dropsy, and with this increase the unpleasant taste disappeared rapidly, and no serious uraemic phenomena developed.

Apathy, slight drowsiness, and a subnormal temperature are the most usual uraemic symptoms present, together with headache and nausea. Vomiting of course occurs, but it is not usually severe, and it is quite exceptional to see cases with the severe vomiting that causes so much difficulty in the treatment of renal disease in civil practice. Epileptiform seizures of a considerable degree of severity are by no means rare, and on several occasions such attacks have occurred quite unexpectedly in the course of the malady, when the general condition of the patient did not suggest that such a serious complication was either imminent or probable. Such cases, however, often show a markedly increased pulse-tension, quite appreciable to the finger, and this increased tension subsides rapidly when the uraemic attack has passed off.

These epileptiform attacks occur in cases of the acute disease where there are no physical signs suggestive of old-standing or latent renal disease, and the

Section of Left Lung. The anterior portion of the upper lobe is congested though aerated; the posterior portion is consolidated, and there are two abscess cavities in the centre of areas of consolidation.

The whole of the lower lobe is occupied by Broncho-pneumonic areas of consolidation, which in many places have broken down into abscess cavities. At the base of the lung a small abscess appears through the Pleura.

The Spleen shows a large abscess cavity at its lower pole,
and along the anterior margin a small cavity has been opened.
Between these two cavities the Spleen is mottled yellow and blue-
grey, and indicates an underlying third abscess. The wall of the
lower abscess is adherent to the colon.
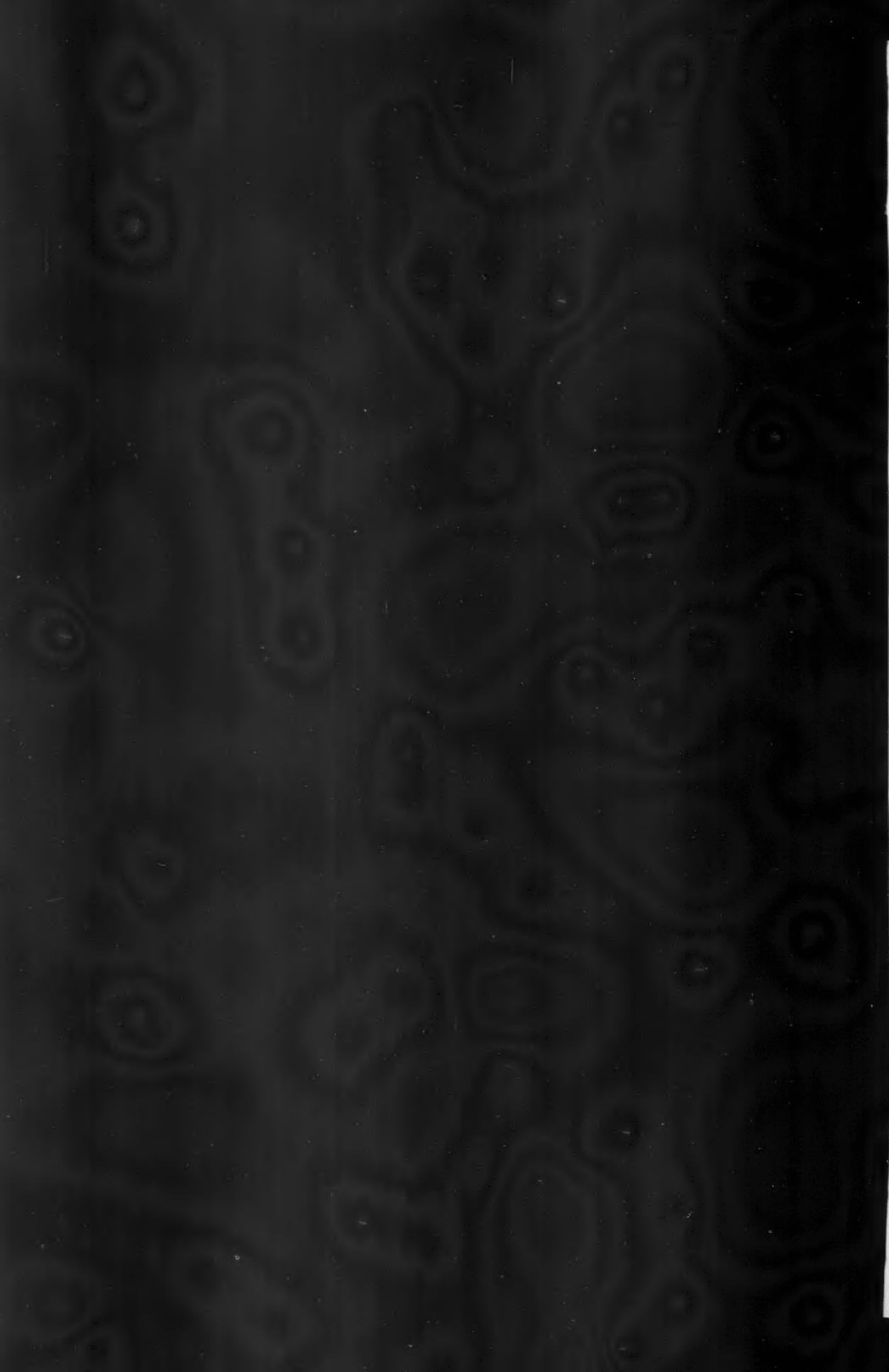
A lower portion of the Ileum shows numerous ulcers from
which the sloughs have completely separated.

A Peyer's patch in the Ileum, showing hyperæmia and
early necrosis.

The Ileum and Cæcum.   The ulcers in the Ileum are deep,
and the sloughs have in part separated.   The Cæcum is riddled
by small ulcers, some of which have coalesced.

There is an ulcer of the Appendix which has a large perforation; the appendicular tissue around the ulcer was apparently healthy.

fact that, notwithstanding their severity, the patient recovers is confirmatory evidence that they are not complications merely occurring in patients the subjects of chronic renal disease aggravated by a superimposed attack of acute nephritis. If this were the case, the prognosis would certainly be more grave. As already mentioned, three fatal cases have fallen under my observation, and in all of these death occurred from uraemia and old renal lesions were present, but the uraemia was of a different type, coma, dyspnoea, &c., being present. In the acute simple cases the epileptiform seizures occur suddenly, at a time when the patient is not markedly uraemic, or at any rate does not present symptoms of the more grave forms of uraemia. They resemble somewhat closely the attacks seen in eclampsia, and also from time to time those seen in ordinary acute nephritis. In one case transitory acute mania occurred after the seizure. Uraemic amaurosis was seen in one case ; it was of a severe type and was accompanied with suppression. The suppression of urine, however, was transitory in its duration, and the next day with its disappearance the amaurosis also cleared up. Headache is a common symptom, and not infrequently it is severe, and is then usually accompanied with high tension. Although dyspnoea, as already mentioned, is of frequent occurrence as an early symptom, the more severe forms of uraemic dyspnoea, such as the well-known hissing type and Cheyne-Stokes breathing, do not occur. In some instances the dyspnoea, although not very marked in amount, has been accompanied by the physical signs of pulmonary oedema, and in a few cases the pulmonary oedema has been quite considerable in degree. In such cases the physical signs of the oedema have been well marked in the upper lobes of the lungs, but this is a well-known phenomenon of pulmonary oedema. No case of death from pulmonary oedema has come under my notice.

In one case extreme dyspnoea of the type known as ' air-hunger ', together with drowsiness, was present, and the dyspnoea was so urgent as to suggest the presence of acetonaemia, but post-mortem examination revealed the existence of old-standing chronic renal disease. The kidneys were extremely atrophied and fibroid, and this case was merely one of uraemia in chronic renal disease and belonged, therefore, to quite a different group from that formed by the bulk of the acute cases now under consideration.

Other uraemic phenomena, such as twitchings, cramps, and the various skin eruptions so common in renal disease, when uraemia is present, have not been present in the cases that have fallen under my observation.

Inflammatory complications, due to secondary infections, were decidedly rare in their occurrence. Bronchitis, however, was common, and in a series of 278 cases was present, either at the time of admission or during the short stay of the patient in a base hospital, in some 30 per cent. of the cases. The more serious pulmonary complications, such as pleurisy and pneumonia, were rare, and no case of pericarditis, associated with nephritis, has fallen under my observation.

Observations on the fundus oculi have been made in a small proportion

of the cases, but no changes of the fundus have been observed in the acute cases. In some of the cases of chronic disease that came under observation as apparent acute cases, the well-known phenomena of albuminuric retinitis were observed.

When the cases are reviewed as a whole, the following conclusions would seem to be justified.

Amongst the very large number of cases that come under observation, there are several distinct groups of cases.

First, there are some cases of ordinary chronic renal disease, of the type described as the granular kidneys occurring amongst the older men. These cases present the ordinary clinical picture of the disease, so familiar to all, breathlessness, swelling of the legs, albuminuria, and yield evidence clinically in the heart and blood-vessels of marked cardio-vascular degeneration. Such cases are almost invariably men over thirty years of age, often much older, who have either rejoined the army after following some civil occupation, or else they are some of the older men who joined the army soon after the commencement of the war. In many of these cases the chronic renal lesion was not necessarily very marked, and, as mentioned above, it is quite probable that under the stress of the campaign it has progressed more rapidly, or an acute nephritis may, in some instances, have been engrafted on the underlying chronic mischief.

Secondly, a group may be recognized, consisting, however, of only a few cases, where very serious chronic renal disease of long standing is present, but where the presence of the kidney disease has not been recognized owing to the absence of urgent symptoms prior to the onset of uremia. Such cases are seen from time to time in all varieties of practice, and hence it is not surprising that a few such cases should have occurred in the army in the field. So far as I can judge, the number of such cases is extraordinarily small; I have not seen more than six, two of which were fatal, the others, although very ill, recovered sufficiently to be evacuated to England.

Thirdly, a group, also small in numbers, might perhaps be made where the clinical picture is essentially similar to that seen in the acute nephritis of civil practice. That is to say, the renal dropsy is much more persistent, as is also the marked albuminuria. Further, such cases develop the well-known anaemia and cachexia of acute Bright's disease.

This third group may be thought to be artificial, as it is possible that such cases are really only more severe examples of the typical cases that constitute the great bulk of the cases.

When these three groups are eliminated, the great bulk of the cases remain and seem to belong to one type, and to a type that, so far as my experience goes, is at any rate not common in civil life. The two outstanding features of the malady are the rapid subsidence of the dropsy and the remarkably low mortality when the severity of some of the uraemic attacks is taken into consideration. Renal dropsy does not usually subside in a week or ten days, and I only know of five deaths in a series of many hundred cases. In two of

these the kidneys were abnormal congenitally, and in two old-standing chronic renal disease was present. In the remaining case a post-mortem examination was not made, so no statement of the exact condition can be made.

An attempt was made to gain further insight into the nature of these cases of nephritis by an analysis of 571 cases where casts were present. In sixty-two of these patients there was apparently a distinct history of a previous attack of renal disease. That is to say, in 10·8 per cent. of the cases the patient gave a history of a previous attack of dropsy similar to that present at the time of observation, or else stated that he had been in hospital or under treatment for ' inflammation of the kidneys' or for ' Bright's disease'. Even if it is admitted that such statements were always reliable, 89 per cent. of the cases gave no such history. Previous renal disease can, therefore, scarcely be the cause of the malady in the majority of instances, although doubtless a previous attack of nephritis is a very important factor in the causation of any given attack of nephritis. It might be urged by some that these cases were really instances of acute nephritis occurring as a complication of slight old-standing lesions of the kidney ; in other words, that the condition was really an acute exacerbation of slight chronic mischief. The fact that many of the earlier cases occurred among the older men gave some support to this hypothesis, and it is probable, I think, that this view is true for some cases, but not for any large number. If all the cases were examined by one observer, and by the same method, it might be possible to obtain a reliable result, but even then it is extremely difficult to differentiate clinically between a primary acute nephritis and one complicating a chronic lesion, unless the signs of the latter are unequivocal. Two cases have already been alluded to in this paper where clinically the diagnosis was confidently made of acute nephritis, yet the post-mortem showed the presence of congenital lesions—hydronephrosis and atrophy in one case, and a single kidney with marked fibrosis in the other, and the acute nephritis was superimposed on these chronic lesions. A considerable number of the cases have an accentuated aortic second sound, and a smaller number show distinct hardening of the radial artery. In a series of 149 cases, accentuation of the aortic sound was said to be present in 39 per cent., and obvious increased tension in and hardening of the radial artery in 27 per cent. of the cases.

On the other hand, in the great majority of cases, there was no evidence either in the physical signs or in the patient's history to suggest the presence of a latent renal lesion. Further, the clinical cause of the malady, and more especially the rapid subsidence of the dropsy and the rapid disappearance of any anaemic complications, are not consonant with the suggestion of an acute nephritis complicating a chronic lesion of the kidney. Such complications are usually most formidable, protracted in their course, and frequently fatal, and it is interesting that, so far as my experience has gone, the fatal cases have shown chronic lesions in all where post-mortem examinations were made. Another method, but an indirect one, available to try and reach a conclusion on this point is to study the age incidence. If the illness were due mainly to the

nephritis affecting men with damaged kidneys, it might be expected that the bulk of the cases would be amongst the older men.

The age incidence in 571 cases where casts were present was as follows :

Under 20 yrs.	20–25 yrs.	25–30 yrs.	30–35 yrs.	35–40 yrs.	40–45 yrs.	45–50 yrs.
24 cases	123 cases	140 cases	126 cases	96 cases	40 cases	22 cases
4·2 %	21·5 %	24·5 %	22 %	16·8 %	7 %	3·8 %

Thus 25·7 per cent. of the cases occur in men under twenty-five years of age, 50·2 per cent. of cases in men under thirty years, and 72·2 per cent. of cases in men under thirty-five years of age. Hence it is clear that large numbers of cases occur in quite young men. After thirty years of age there is a slight drop in the number of cases, and this drop becomes more marked after thirty-five years of age. In order to deduce really conclusive results, it would be necessary to know the number of men of the ages mentioned in the troops, as it is of course obvious that although only 7 per cent. of the cases occurred in men between forty and forty-five years of age, and nearly 25 per cent. in men between twenty-five and thirty years, yet it is quite possible that the actual incidence of the malady was higher in the older than in the younger men, since the number of the older men in the ranks is probably very much less. It has not been possible to get any accurate information as to the age of the troops as a whole, but I am informed that the great bulk of the men are under thirty-five years of age.

The conclusions are probably warranted that the malady affects men of all ages, that young men are certainly affected in large numbers, and that possibly the actual case incidence may be higher in the older men, but the actual statistics available at the moment do not afford certain proof of this.

The men affected belong to all branches of the service, and although the great bulk of the cases have occurred in men at the front, the malady has been by no means limited to those actually serving in the trenches. Men serving in the Army Service Corps and engaged in transport and supply duties, and men in the ammunition columns, have frequently suffered. Many of these men, although not actually serving in the trenches, have been engaged in duties involving much exposure to severe climatic conditions both by day and by night. Similarly a number of R.A.M.C. orderlies at the front have been affected. The disease has, however, not been limited to the men serving at the front, and has occurred amongst men serving entirely at the bases, who have never been to the front. Further, there have been several cases affecting R.A.M.C. orderlies whose duties have been confined entirely to base hospitals located in good buildings, where there has not been any question of exposure. In a series of 332 cases, 285 cases occurred in men serving at the front, and 25 cases in men whose duties retained them at the base. In the remaining 22 cases no details of service were recorded. Thus it is clear that the malady is not confined to those exposed to the vicissitudes of the actual front. The number of officers affected has been very small, and in the earlier months of the outbreak a large series of cases

occurred amongst the rank and file without any case in an officer falling under my notice; later, some cases occurred amongst officers. These were not limited to the more senior officers; some occurred in the younger men and some in the older. Up to the present time, about 1 per cent. of the cases have occurred amongst officers. The cases were of the same character as those seen in the men. In some there was distinct clinical evidence of old-standing renal disease, or of cardio-vascular degeneration. In others the cases were of the acute type described above, where the dropsy subsided rapidly and the albuminuria more slowly. Uraemic manifestations were sometimes present, and in one case uraemic epileptiform seizures that occurred quite suddenly, in a case of apparently no great severity, were followed by acute maniacal excitement. This, however, was also quite transitory, and the following day the patient was quite rational and had only a vague recollection of the seizure. In this case, as in others, the epileptiform seizure was preceded by a period of intense headache. There was no evidence of previous renal disease in this case, the only one, so far as I know, that presented that rather rare symptom of uraemia—mania.

One of the most striking features of the outbreak of nephritis was that it was confined to the British troops of the Expeditionary Force. It practically did not occur in the Indian troops, as I only know of three cases of nephritis having occurred amongst them. Three large Indian base hospitals, containing in all several thousand beds, were frequently visited by me, and I only saw, in a period extending over twelve months, one case, and this was extremely slight, some albuminuria but no dropsy being present. Two other cases were reported on the case-sheets. This absence of the disease amongst the Indian troops is very striking, as these troops suffered in common with the British troops from other maladies commonly attributed to exposure. Thus, during the winter of 1914 and early spring of 1915, large numbers of cases of so-called frost-bite and trench foot occurred amongst the native Indian troops, and their hospitals contained large numbers of cases of bronchitis, dry pleurisy, and various forms of pneumonia. Bronchitis was especially prevalent and was often of a severe type, but yet nephritis and renal dropsy did not occur.

Some observations were also made on the question whether the incidence of the disease was materially affected by the length of time the men had served in France. In a series of 332 cases, data were available in 326 cases, and, as is seen, the results are not very definite; 195 cases occurred in men who had served six months or less in France, and 131 cases in men who had served from seven to twelve months. A small number of cases occurred in men who had only been out a month or less—in one case only one week. It is difficult to interpret these results, owing to the numerous possible fallacies. Thus the number of men who had only been in France a short time would in certain months be suddenly greatly increased owing to the arrival of fresh troops, and it is probable that the only deduction that is justifiable is that a considerable proportion of the cases occurred in men who had been serving from two to five months in France.

Whether or no the malady had a greater incidence in those who had served ten and eleven months is uncertain, but in view of the smaller numbers of these men in the field it is possible.

Number of months served in France	1	2	3	4	5	6	7	8	9	10	11	12
Number of cases of nephritis	16	43	49	32	37	18	18	20	14	31	40	8

Total	6 months or less	195
	Over 6 months	131
Grand Total	. . . .	326

In one case the malady is said to have recurred, and this is probably correct, since the patient was invalided home after a slight attack and was discharged with the urine free from albumin. After a short furlough he was sent out to France again and there contracted another attack with oedema and albuminuria, but this attack also was not of great severity, and the dropsy speedily subsided. The causation of the disease is obscure. Modern views regard nephritis as usually produced by some toxic agency, and especially as the result of an infection, but the infection is often one that produces so little illness that it is overlooked. A series of 278 cases were analysed to try and ascertain whether any illness, slight or severe, had preceded the onset of the dropsy. In 10·4 per cent. of these cases a history of a severe ‘ cold ’, or of ‘ diarrhoea ’, or of ‘ influenza ’, or ‘ sore throat ’ was elicited, and after a few days of illness the dropsy was noticed, but in the remaining 89 per cent. no such symptoms were noticed. On the other hand, in eighty-five cases, i. e. 30 per cent., the patients gave a history of and had distinct signs and symptoms of bronchitis, either at the actual onset or in the early stages of the nephritis when they came under observation in hospital. In some cases the bronchitis was quite severe. Bronchitis, so far as my experience goes, is the only frequent illness prior to the onset of the dropsy, and the bronchitis itself is of the acute type and rapidly followed or accompanied by the nephritis. Tonsillitis preceding the nephritis is very rare, and this was an unexpected result, since it is a well-known recognized cause of nephritis.

A plausible hypothesis might be advanced that the nephritis is causally related to the bronchitis were it not for the fact that bronchitis was common in the Indian troops and that in them no nephritis occurred. Notwithstanding this difficulty I am inclined to view the cases of acute nephritis described in this paper as due to some infection, the infecting agent causing in the first place in many cases some illness such as bronchitis, severe cold, diarrhoea, &c.

Some writers might see in this outbreak of nephritis evidence in favour of the disease being directly due to cold and exposure. Others, seeing the gross contamination of the soil in the field of operations, might seek a cause in a microbic infection of the urinary tract. Such observations as have as yet been made on this point have not yielded concordant results, and the fact that the disease has occurred also at the bases is not in accord with this view.

Pending further observations on the causation of the malady, it may be said that clinically it is a distinct nephritis, characterized (1) by the rapid subsidence of well-marked renal dropsy; (2) by the frequent presence of bronchitis and dyspnoea; (3) by the severity and suddenness of onset of uraemic manifestations such as epileptiform seizures; (4) by the rarity of occurrence of inflammatory complications; and (5) by the extraordinarily low mortality, i. e. between 0·3 and 0·4 per cent. as determined from the total number of cases that have occurred up to the present time. Although the uraemia convulsions are severe when they occur, yet their occurrence is exceptional.

CRITICAL REVIEW

THE PROTECTIVE FERMENTS OF THE BODY

By R. L. MACKENZIE WALLIS

Introduction.

THE past few years have witnessed a remarkable growth in our knowledge of the mechanism of defence of the animal organism against disease organisms or their toxic products. Ever since the discovery that the serum elaborates reaction bodies (immune substances) against a variety of foreign bodies (antigens) introduced into it, numbers of experiments have been devised and almost as many theories invoked to explain their nature and action. It is beyond the scope of this article to review all the various phases in the elucidation of the problems of immunity, many of which still remain unsolved, and in consequence only one special form will be discussed, namely, the production of protective ferments, and their influence on the processes of immunity and metabolism. The evolution of this idea of a definite chemical mechanism of defence is due to the extensive investigations of Abderhalden (1) and his collaborators spread over a number of years. In order to study the action of such protective ferments in the blood Abderhalden has devised two tests by means of which the chemical changes which such ferments induce are capable of detection outside the body. These tests depend for their reliability upon two main principles, namely, the existence of definite ferments in the blood-stream, and their absolute specificity. The object of this paper is therefore to review as far as possible the work that has been done during the past few years upon this subject, and to ascertain whether the claims of Abderhalden can be regarded as justifiable in the light of this accumulated knowledge.

General Considerations.

The whole subject would appear to be of paramount importance in the elucidation of some of the many problems of immunity which still await solution, more particularly as it embodies the application of the principles of immunity to the body cells themselves. Not only do we endeavour by this means to ascertain the chemical changes which each individual cell or groups of cells undergo, but we hope also to correlate structure with function much more closely than has

hitherto been possible. We have many examples in the human body of such a relationship, and reference need only be made to the liver cells, which produce bile, or the cells in the medulla of the suprarenal bodies, which elaborate the active principle adrenalin. Each cell has its own part to play in the economy of the organism, and possesses its own special structure, chemical composition, and functions. Consequently, we should expect to find that the body cells only take up substances from the blood-stream which are necessary for their own particular function. The appearance of any foreign substance or foreign cell in the blood-stream would be of no use to the cells as such, unless previously destroyed by some active chemical agent. In order, therefore, to remove these bodies special ferments are elaborated, and upon this change the principles of the Abderhalden tests for diagnostic purposes are based. In order to comprehend more fully the chemical changes which these specific ferments induce we must turn our attention to the more minute processes of protein ' digestion ', which can be followed in the gastro-intestinal tract, and also in experiments *in vitro*. The pepsin in the gastric juice attacks the proteins in the food-stuffs in the presence of hydrochloric acid, breaking them up into albumoses and peptones. These latter substances are further attacked by the trypsin in the pancreatic juice, and the erepsin in the intestinal secretion, with the formation of various peptides and amino-acids. The proteins in the food are therefore reduced by ferments in the alimentary tract, and the final products—the amino-acids—constitute the building-stones or the ' Bausteine ' of Abderhalden. These building-stones are absorbed into the blood-stream, and the cell takes from the blood amino-acids in proportion to its individual requirements. Over this absorption and distribution of amino-acids the liver exerts a protective influence, preventing any foreign elements from passing into the circulation in the form of undigested proteins. It also controls the quantity of those amino-acids entering the blood-stream. The lymphatic system similarly exerts a protective influence by preventing the entrance of body cells into the circulation. The existence of such defensive mechanisms would explain the constancy of composition of the blood.

Physiological Considerations.

The principle of Abderhalden's tests, as applied to pathological processes, has for its basis the fact that the introduction of foreign substances into the blood-stream excites the production of specific ferments in order to destroy them. Consequently we should expect that the injection of foreign materials from the alimentary tract would result in the production of ferment changes in the blood which have a special character according to the chemical nature of the body introduced. Observations of this kind have been made by Abderhalden, and the results would appear to support his main contentions.

For example, cane sugar is said to undergo decomposition when introduced as such into the blood by way of the intestinal tract. It is quite easy to demon-

strate the change which takes place by means of a good polarimeter, since the optical effects are so well marked. To give an example : the blood of an animal is taken and the serum mixed with a solution of cane sugar. The polarimeter shows that the cane sugar remains unchanged. The following day 5 grm. of cane sugar are given intravenously, and a sample of blood taken twenty-four hours later. The serum, when mixed with the cane-sugar solution, showed an original rotation of $+ 0.45°$, but forty-five hours afterwards the rotation was $-0.50°$. From this experiment we must conclude that the cane sugar has excited the production of the ferment invertin which destroys it, thus preventing it from being excreted unchanged by the kidneys. This experiment, however, very frequently fails, and we are quite unable to detect any such invertase in the blood serum. The same applies to injections of lactose, and I have been unable on some occasions to detect any ferment in the blood serum capable of digesting lactose under such conditions. These observations apply in a like manner to practically all carbohydrates, and many investigators, including Abderhalden himself, admit that the evidence of specific ferments against carbohydrates is lacking. With the monosaccharides and disaccharides this discrepancy may be partly explained by the fact that the normal kidney rapidly eliminates such substances in an unchanged form, and since they are not retained in the blood-stream there is no need for the production of protective ferments to destroy them. Abderhalden would claim that these bodies are not ' disharmonious ' substances like proteins, and consequently do not call for a destructive ferment. The conditions are totally different, however, when soluble starch is injected into the circulation. Abderhalden states that the serum is able to digest cane sugar, and concludes that the disharmonious starch leads to the appearance of a ferment not exclusively directed against the starch itself. Now Abderhalden appears entirely to overlook the fact that there is a ferment existing preformed in the blood which is capable of digesting starch, namely, diastase. This diastase is constantly present in the blood in definite quantity, and undergoes considerable alteration in disease, particularly in pancreatic lesions. If starch is injected into the circulation no definite increase in the diastase content of the serum can be detected, yet the starch rapidly disappears. Similar observations have been made by King (2) in America, and it appears that in this case we have an explanation of the results recorded by Abderhalden. The same lack of production of protective enzymes follows the injection of the five-carbon sugar raffinose. Altogether it would appear that we can find no definite support to Abderhalden's claims as applied to the carbohydrates.

Another similar phenomenon is the observed increase of fat-splitting power of the serum after an excessive absorption of fat from the intestine. Every one is no doubt familiar with the milky serum which frequently occurs after a meal rich in fat, and I have been able to investigate the changes which take place in such sera by means of the polarimeter, and stalagmometer. The fat which accounts for the opalescence of the serum rapidly disappears with accumulation of the resulting products in the serum. The chemical alterations which take

place may profoundly modify the physical character of the serum, and this point should receive attention in all work upon blood sera.

The oft-quoted experiment of giving large quantities of egg albumin by the mouth and obtaining it in an unaltered form in the urine has not been corroborated by recent workers upon the subject. This experiment I have myself repeated, and by the use of a new and delicate test for egg albumin have been unable to detect its presence in the urine even after the ingestion of very large quantities. Examination of the blood serum, however, clearly demonstrated that some substance was present which would digest egg albumin, and egg albumin only, and that this was not previously present. Abderhalden has demonstrated by the polarimeter method that injections of various albumins, silk peptone, and even the vegetable proteins—gliadin and edestin—give rise to specific ferments when injected into animals. If, however, we apply the same tests to proteins of less complex structure we find that no such protective mechanism exists. For example, the injection of the simple protein salmin into an animal does not excite the production of a ferment capable of digesting this protein. This might, of course, be explained by stating that such a substance is not disharmonious, or that it is too far removed from the complex proteins to give a reaction. Yet Abderhalden claims to have demonstrated the presence of a specific ferment after the injection of silk peptone, a substance quite as foreign as salmin to the body and probably less complex. Further, it is found that the introduction of foreign proteins leads to the appearance of a ferment in the blood which will digest proteins other than the one introduced. On the other hand, some observers have entirely failed to verify the experiments of Abderhalden as quoted above. The criticism adduced against the whole theory based upon negative results obtained by the injection of artificially prepared products is probably quite unjustifiable. We know quite well how normal products of the body cells undergo considerable modifications when dislodged from their normal habitat. The bile salts, for example, are actively haemolytic, yet we find these substances circulating in the blood in quantity in certain types of jaundice, although there is no evidence of haemolysis. Again, these same bile salts appear in the urine, but such a urine gives no evidence of haemolytic action. We must assume, therefore, that either an antibody is formed in the blood, or that the bile salts are stripped of the particular linkage on which this special property depends. The latter seems to be the most likely explanation. The same observations apply in the case of nephritis. The albumin excreted in the urine in certain forms of this disease is, according to my own observations, a distinct substance differing in chemical and physical properties from the serum proteins. When injected into animals it is excreted unchanged, and does not exert any specific effect, e.g. the production of protective ferments, or precipitin formation. This protein is absolutely inert, and this change, I believe, has taken place in the kidney itself. The kidney therefore appears to play an active part in stripping the protein of the serum of certain active linkages and thus rendering it inert, and consequently of no use to the animal economy. The same process, however, does not apply in

all forms of nephritis, and there are also some types of albuminuria which are quite distinct. It appears highly probable that the failure to produce specific protective ferments in the blood may be due to the same factors, and, consequently, does not militate against the occurrence of such ferments. The question also of the production of anaphylaxis, or hypersensitivity, might be thought to be explained by this means, since we know that foreign substances introduced into the body give rise to this change. For example, the kidney tissue of a dog when introduced into the circulation of the same species results in the production of a ferment capable of digesting kidney tissue. The foreign substance in this case is broken down and then loses its individuality, and also its specificity. There is no doubt that these ferments do bear some relation to the protective ferments of Abderhalden, but other factors undoubtedly come into play, some of which will be discussed later in this paper.

The Methods of applying the Tests for the Detection of Protective Ferments.

Two chief tests have been devised for the diagnosis of pregnancy and also pathological conditions, and the detailed application of these tests to the diagnosis of pregnancy is given below.

The optical test. The growing placenta is regarded as the agent providing the foreign protein substances which excite the production of a protective ferment in the maternal blood-stream. Owing to its proteolytic nature we are enabled to recognize the breakdown products, and these are the essential factors in both the tests that are to be described. The materials necessary are, first of all, the blood serum of the patient to be examined, and a supply of fresh human placenta. The optical test requires the use of a good polarimeter capable of giving readings below 0·01°, and in addition a special polarimeter tube box for maintaining a constant temperature. After some practice the readings are readily made, and differences of rotation determined. The material used for the substrate upon which the ferment in the serum of pregnant women acts is a solution of placental peptone. This is prepared by the digestion of placental proteins with acids, the hydrolysis being allowed to proceed to the stage of peptones, and then arrested. The placental peptone is prepared as follows : fresh human placenta is carefully washed free from blood with salt solution, and then thoroughly macerated. The residue is then treated with sulphuric acid, and allowed to remain at room temperature for four days. The acid slowly hydrolyses the proteins present, and this change is arrested on the fourth day by the addition of several volumes of distilled water. The sulphuric acid is then neutralized by the quantitative addition of baryta water, and the resulting dense white precipitate removed by filtration. This barium sulphate precipitate is ground up in a mortar with distilled water, and the decanted and filtered extracts collected. The extracts must now be carefully freed from all traces of acid and barium hydrate, as otherwise the hydrolysis would proceed further, and the yield of peptone be diminished considerably. The extract is now concentrated in a large distilling

flask heated over a water bath, and in order to prevent frothing the peptone mixture is introduced in small quantities at a time. A thick syrup possessing a yellow colour finally results, and this is dissolved up in warm methyl alcohol. The placental peptone may then be thrown out of solution by absolute alcohol as a fine yellow powder, which is readily soluble in water. For the polarimeter test, a 5 per cent. solution of this peptone in salt solution is used, and this is placed in a sterile flask and kept sterilized ready for use. All the materials used throughout the work are also sterilized.

Into the polarimeter tube 1 c.c. of the placental peptone solution is placed, and 1 c.c. of the clear serum to be tested. The remaining space is filled with salt solution, and the tube is now ready for insertion into the polarimeter. The solution always shows a laevo rotation, and the actual rotation is noted. The tube is replaced in the incubator and examined at intervals of from six to eight hours, the examinations not extending beyond forty-eight hours in all. As far as possible it is advisable to use the same volume of the serum in every test, and the size of the polarimeter tube must not be altered, as otherwise comparable results are not obtained. The splitting of the placental peptone into amino-acids produces an alteration in the optical activity of the solution, and the amount of rotation gives an indication of the activity of the ferment present in the serum. A difference of rotation below $0.05°$ is disregarded, the serum of pregnant women usually producing a rotation of at least $0.2°$ and even higher.

The dialysation method. The optical method has been proved by Abder-halden to demonstrate the presence of a specific ferment in the blood of pregnant animals. The dialysation method has consequently been devised to detect the end products resulting from the splitting of placental protein outside the body. For the dialysation test a preparation of placental tissue is required, and this is prepared in the following way : a fresh placenta from a normal case of labour is obtained, and carefully cleaned with water or saline. The foetal surface and also the membranes are cut away, and the remaining tissue cut up in small pieces and washed in running tap-water until every portion is quite white. This washing is absolutely necessary as the placental tissue must be quite free from blood before use. The pieces of tissue are then placed in a large basin contain-ing about ten times their volume of distilled water with two drops of glacial acetic acid, and are then thoroughly boiled for ten minutes to coagulate the proteins present. The coagulated placental albumin is thoroughly washed with cold distilled water, and then again boiled in the same volume of water as before. The water is now tested with the ninhydrin reagent to determine whether any dialysable substances are still present in the placental tissue, as these would produce a serious error and completely invalidate the test. The ninhydrin test is made upon 10 c.c. of the water with 0.2 c.c. of a 1 per cent. solution of ninhydrin, the mixture being boiled for one minute. A positive test, i. e. a blue colour, points to the presence of dialysable substances, but in most cases these are usually absent at this stage. The tissue is again washed in distilled water, and then heated with five times its volume of distilled water. In order to detect

even smaller amounts of dialysable substances 5 c.c. of the water are tested with 1 c.c. of ninhydrin solution, the test being frequently positive with this amount. The distilled water generally contains small fragments of placental tissue, so that before applying the ninhydrin test to any sample of the washings, it is first of all necessary to filter. When the ninhydrin test proves negative the placental tissue is placed in a glass vessel containing chloroform water, covered with a layer of toluol, and stored in a cool place until required. The tissue before actual use on a test is again subjected to boiling in five times its volume of distilled water until a negative ninhydrin reaction is obtained. It is only in this way that we can exclude dialysable substances in the placental preparation which interfere with the test. The writer has also found it necessary to make fresh preparations of placental tissue at frequent intervals as the stock material cannot always be relied upon. The placental tissue is obviously one of the most important factors in the test and the greatest source of error, hence the necessity for exercising the utmost care during the steps in its preparation. The dialysers used in the test are those specially prepared by Schleicher and Schull, and labelled No. 579 A, the size most suitable for ordinary use being 16 by 50 mm. These dialysers are allowed to soak in distilled water containing toluol for some days, and then tested as to their capability of separating peptones and amino-acids from colloidal substances. For this purpose a preparation of peptone is required, that used by Abderhalden being the 'seiden' peptone.

The writer has used a peptone solution made from 'Darby's fluid meat'. Five cubic centimetres of a 0·1 solution of peptone are placed in a dialyser tube, and surrounded by 20 c.c. of distilled water contained in a special glass vessel, all the materials being previously sterilized. The vessel is then placed in an incubator for sixteen to twenty-four hours, and then 10 c.c. of the dialysate tested with 0·2 c.c. of a 1 per cent. solution of ninhydrin. A dialysing tube giving a moderate blue colour is accepted as reliable, those giving either a very strong reaction or a negative result being discarded. After passing this test they are carefully washed in distilled water for some weeks and tested in the same way with serum albumin or egg albumin, only those giving a negative ninhydrin test being used. The dialysers can be used repeatedly, provided they are subjected to careful washing after each test, and stored in distilled water containing toluol as a preservative. The glass vessels used for the test are provided with ground-glass stoppers and are easily sterilized. They should be of such a size that when the dialyser is in place there is a space of 0·5 cm. between the dialyser and the vessel wall. For the test the glass vessel contains 20 c.c. of sterile distilled water covered with a layer of toluol. The serum for the test is obtained in the same way as described for the polarimeter test, and must be quite fresh, as the slightest haemolysis in the serum is sufficient to produce an erroneous result. The removal of 10 to 15 c.c. of the patient's blood from the median basilic vein, when carried out with the usual precautions, and the transference of the blood directly into a sterile centrifuge tube, generally avoid these sources of error. Since the blood serum may

contain dialysable substances in the form of amino-acids after meals, it is always advisable to remove the blood from a fasting subject. The writer has also found it preferable to take the blood in the evening, as the dialysable substances tend to be reduced in amount when the body is fatigued. The ninhydrin reagent (triketohydrindene hydrate) is now manufactured and sold in 0·1 grm. tubes, in the form of a yellowish-coloured salt, which is readily soluble in water, giving a colourless solution. The solution used in the dialysation test is made up to a strength of 1 per cent. This compound reacts with any amino compound where the amino group is in the a-position to the carboxyl group, and the resulting condensation compound possesses a blue or violet colour. The ninhydrin solution should be kept in the dark and properly sealed, as the reagent rapidly deteriorates ; and further, it is advisable not to keep the solution longer than one week.

Method of applying the dialysation test. A series such as the following is made up in carrying out the test for the diagnosis of pregnancy :

(1) Serum of patient (1 c.c.).

(2) Serum of non-pregnant woman (1 c.c.).

(3) Heated placental tissue (about 1 grm.).

(4) Heated placental tissue + 1 c.c. serum of patient.

(5) Heated placental tissue + 1 c.c. serum of non-pregnant patient.

(6) Heated placental tissue + 1 c.c. serum of patient, heated to 60° C. for 30 minutes.

In the actual tests 1 c.c. of serum is placed in a properly tested dialyser together with a small quantity of the placental tissue, and the dialyser surrounded by 20 c.c. of sterile distilled water, toluol being added to both. The whole series of tests, as given above, are placed in the incubator at 37° C., and allowed to remain for sixteen to twenty-four hours. At the end of this time they are taken out and the dialysates examined separately with the ninhydrin reagent. During the earlier stages of this work the biuret test was used to demonstrate the presence of peptones in the dialysate, but since the introduction of the much more delicate reagent of Ruhemann known as ninhydrin, the former test has been discarded. To carry out the biuret test, a solution possessing only a faint blue colour, made up from a 30 per cent. solution of sodium hydrate and a very dilute solution of copper sulphate, is used. The solution is placed in a reagent glass, and the addition of the dialysate produces a blue ring at the junction of the fluids. Test No. 4, however, should always give a reddish-violet colour indicating a positive reaction.

The ninhydrin test, on the other hand, owing to its extreme delicacy, requires much more careful manipulation, and, further, is full of many pitfalls. Ninhydrin, or triketohydrindene hydrate, when heated with peptones and amino-acids, forms condensation compounds which possess an intense blue colour.

The sensitiveness of this reagent depends upon the concentration of the reacting substances present, and will show the presence of the amino-acid glycin in 1 part in 65,000 of water, and 1 part of the other amino-acids in 15,000 to

25,000 of water. Further, every protein and protein-containing material will, on dialysis, give this test—e. g. fresh milk, saliva, urine, blood plasma, lymph, sweat, fresh and boiled egg white, fresh and cooked meat, although containing no biuret-yielding bodies. From this list of substances alone it will be clear that all proteins must be purified by dialysis before use. Further, the materials used in the test must not be handled with the fingers, and pipettes must not be placed in the mouth, owing to the danger of contamination with the sweat and saliva respectively. Since haemoglobin is a diffusible protein when free, it follows that haemolysed serum cannot be used for the diagnosis of pregnancy.

The solution is made up in distilled water to the strength of 1 per cent., and it is advisable to use moderately fresh solutions as the reagent does not keep well. To carry out the test 10 c.c. of the dialysate are placed in a clean sterile boiling-tube, and 0·2 c.c. of ninhydrin solution added. The mixture is then boiled for one minute, a boiling-stick being inserted to prevent frothing. A positive result is indicated when the solution assumes a blue colour. Carried out in this way the dialysation method gives results which always confirm the optical tests, and provided attention is paid to the details of technique, the test is of value in the diagnosis of pregnancy. Alone, however, the test cannot be said to be of absolute value, as there are still fallacies over which we have no control. As shown above, the sensitiveness of the reagent depends upon the concentration of the reacting substances. Now, if we assume that one unit of substance is required to give the blue colour, the dialysate from the serum of pregnant women must contain one unit or above to give a positive test. In the crucial test we are using two materials, namely, serum and placental extract. The serum alone may only contain 0·5 unit, and so give a negative reaction when dialysed alone, and similarly the placental tissue may yield 0·5 unit. When, however, the two are mixed together one unit of dialysable substance is obtained without any actual ferment changes taking place, and a positive test results. Again, a serum which has been obtained after a meal will contain an increase of diffusible substances, as much possibly as 0·9 unit, and this, when mixed with the placental tissue, will also give a positive test. Such results have been met with, and a number of experiments have been made in an attempt to eliminate this error. To a certain extent this possible source of error is overcome by inactivation of the serum, as in experiment (6) in the series given above. All that can be said at present is that certain definite rules must be laid down before applying the test. In the first place, the patient must have abstained from food at least four hours previously, and the blood is best taken late in the day, as when the body is fatigued the blood contains less of these diffusible substances giving the ninhydrin reaction. The placental tissue also requires careful preparation, and particularly long-continued dialysis before use.

The sensitiveness of the ninhydrin reaction depends upon the concentration of the dialysate, and also of the reagent itself. The dialysate from all the tests therefore requires boiling for exactly one minute, and the same gas-flame must

be used so that evaporation is constant in all. The best method of checking this is to use specially graduated test-tubes for the ninhydrin test, and the amount of fluid left in each tube after boiling should be compared.

The Question of the Specificity of the Protective Ferments.

We have seen that there is some evidence from physiological investigations pointing to the fact that protective ferments are produced as the result of the stimulus set up by foreign substances invading the blood-stream. The chief point of interest is that these substances are chiefly protein in nature, more especially of complicated types. All substances foreign to the particular animal are of this nature, whether they be represented by bacteria, toxins, vegetable products, tissues, or tissue constituents of other animals. In consequence attention must be paid to the proteins in a consideration of these protective ferments, and we will consider the available evidence at the present moment in favour of their specificity.

Since Abderhalden first applied his theory to practical medicine for the diagnosis of pregnancy, we may first briefly review the results obtained (3) in that condition. Schmorl, Veit, and Weichardt have demonstrated that chorionic epithelium entered the circulation during pregnancy, but at the time they were not aware that chorionic villi were present in the fertilized ovum in the first month of gestation. This latter point has, however, been clearly demonstrated by Peters, Stahl and Beneke, Brice and Teacher. The presence of chorionic villi in the circulating blood should excite the production of a specific ferment, and the serum of a pregnant woman should be capable of digesting placental protein. This has been found actually to occur, and a large volume of literature has appeared from all parts of the world dealing with this particular ferment and its detection outside the body. That placental tissue does play a prominent part in the production of a protective ferment has been shown conclusively by a number of animal experiments (4). The serum of a pregnant woman can be inactivated by heating to 60° C. for half an hour, thus demonstrating that the body in question is destroyed by exposure to this temperature. An extract of human placental tissue in salt solution and also human placental peptone was injected into dogs, rabbits, and guinea-pigs, either intravenously or intra-peritoneally, the blood of normal animals mixed with placental peptone being also used. In the case of dogs, two injections of 1 gr. of placental peptone were given on successive days, the blood collected eight days afterwards, and the serum tested against placental peptone by the optical method. In every case a breakdown of the placental peptone occurred. The rabbits received four intravenous injections of 2 to 3·5 c.c. of placental extract, and six days afterwards the serum when tested gave a similar result. The same changes occurred in guinea-pigs after injections of 0·6 c.c. of placental extract into a skin vein. These experiments proved that a ferment or ferment-like body was present in the blood-stream, capable of detection by the optical method and the dialysation

test. Abderhalden has reported the results of over 600 tests made in his laboratory by the optical and dialysis tests with only one or two errors.

Since the original publication of Abderhalden a vast literature has already accumulated on the question of the diagnosis of pregnancy. It is quite impossible to refer in detail to all these communications, the greater bulk of which support Abderhalden's views. There is no doubt whatever that the diagnosis of pregnancy is one which is peculiarly favourable for acquiring a working knowledge of the technique of the tests employed. The materials are easy to obtain, and the results are always confirmed or disproved, since it is a condition which admits of no error in diagnosis. Apart from its value in demonstrating the principles and mode of application of the methods it is not of any great clinical import. The occurrence of a positive reaction in the third week of pregnancy has been demonstrated by Hirschfeld (5) and Piorkowski (6), whilst Markus (7) actually obtained a positive test ten days after the last menstrual period. Schlimpert and Hendry (8) report positive results in twenty-eight pregnant women who had missed one period by about four days only. The presence of the ferment in the blood serum has been detected throughout pregnancy by a large number of investigators, and it is found to persist for some days after labour. Engelmann (9), Franz and Jarisch (10), Maccabruni (11), all report cases in the puerperium giving reactions three weeks after labour. In extra-uterine pregnancy the test would appear to be of some clinical value, and cases of this nature giving positive reactions have been recorded by Ebeler (12), Henkel (13), Tschudnowsky (14), Ekler (15), Williamson and Wallis (16). The differentiation between myoma and pregnancy, amenorrhoea in the climacteric, and other conditions associated with pregnancy have also received attention generally with satisfactory results. Perhaps the most interesting condition where a positive reaction is obtained with placental tissue is that of chorion epithelioma as demonstrated by Paltauf (17), Franz and Jarisch (10), Williamson and Wallis (16). A more recent development of the Abderhalden methods for the diagnosis of pregnancy is attributed to Kiutsi. He finds it possible to detect the placental destroying ferment in the urine of pregnant women by the use of specially prepared placental tissue. His results are certainly striking, but must be received with caution. Malone (18), however, has worked out the urinary test, and appears to obtain satisfactory results in pregnancy, and only future work will decide whether this method is generally applicable. The perusal of the literature on this subject, together with the writer's own experience, would lead him to suppose that there is a placental splitting ferment in the blood of pregnant women, and proof is forthcoming not only from a record of the cases investigated by the authors quoted above, but also from pure experimental work. There is, however, on the other side of the balance a very large and increasing volume of observations tending entirely to disprove the occurrence of a specific ferment capable of attacking placental tissue, and placental tissue alone. Many of these observers find the method of detecting this ferment unreliable, and report gross errors in diagnosis. Some, again, have found their

technique faulty, and after subsequent rectification obtain satisfactory results. With very few exceptions the principle on which the test is based is undisputed, and only the mode of application thereof is assailed. The workers under this heading have been severely criticized by Abderhalden, in many cases unjustly, since nothing is easier than to find fault with their technique. In reality the method when carried out with the ordinary care is really quite simple, and open to any trained laboratory worker to perform. Too often, however, it is apparent that anxiety to put into print results obtained on insufficient knowledge and precision has led to the erroneous results. The writer himself began the work with a distinct bias against the tests, and this was enhanced by his earlier experience in the diagnosis of pregnancy. Only after eighteen months of patient work was he able to obtain fairly reliable results, although it is true this work was done when very little was known about the tests and their pitfalls. This was followed by a period of successful results which were so remarkable as to make him a convert to Abderhalden's views. Since the chief criticism has been directed against the specificity of the protective ferments the discussion on this point will be referred to later in this review.

The fact that placental albumin is capable of producing a specific ferment in the blood at once led workers into the field of malignant disease with the object of applying the principle to the diagnosis of cancer. Here, however, there has been very little success, although some observers have reported striking results, particularly Abderhalden (1), Epstein (19), Gambaroff (20), and Brockman (21). On the other hand, a number of pathologists have completely failed to verify the presence of a ferment capable of digesting cancer tissue, whilst others again find that the ferments present are not specific for this tissue alone. Amongst these are Lindig (22), Frank and Heimann (23), Engelhorn (24), and Leitch (25) and Bulloch (26) in this country. There is no fault to find with their technique, and their results appear to be quite conclusive. The investigations have, however, not been so extensive as in the case of the diagnosis of pregnancy, and probably it is too early to warrant any definite statement either for or against the presence of a specific ferment or ferments in malignant disease. It would appear that some early cases do not react at all to one form of carcinoma tissue, and it may be that we shall require to investigate the reactions to all the various histological types before coming to any conclusions. Thus the serum from a case of columnar-celled carcinoma of the stomach may not contain a ferment capable of digesting a spheroidal-celled carcinoma when used for the test, but will digest the columnar-celled tissue. Abderhalden, however, is quite convinced that his tests hold good for malignant disease, and reports that he is now engaged in preparing a serum for therapeutic purposes based upon his findings. In this connexion it is of interest to note that Brockman, working in my laboratory, found much more strongly positive reactions in the earlier stages of malignant disease than in the later stages, where cachexia was well marked.

In various other fields the claims of Abderhalden have been supported

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by most striking results, and this particularly in diseases of the ductless glands.

Lampe (27) has demonstrated the occurrence of specific ferments in the serum of patients with exophthalmic goitre capable of digesting exophthalmic goitre tissue, thymus tissue, and also ovarian or testicular tissue, and his results have been confirmed by Kolb (28) and Bauer (29). These observations would therefore tend to show that exophthalmic goitre is due not to hyperthyroidism, but rather to a malfunction of the thyroid gland, since only thyroid tissue from a case of exophthalmic goitre is broken up, whereas normal thyroid tissue remains unchanged. Further, the thymus and generative organs would appear to have some relation to the origin of the disease, and we know that the thymus is frequently enlarged in exophthalmic goitre.

Similarly with regard to diseases of the thymus, good results have been reported by Bauer, and Ludlum and White (30). The latter found that three cases of lymphatism reacted to thymus tissue, and also a case of infantilism. They also report a case of gigantism in a girl of five years whose serum reacted to pituitary tissue. The pituitary body and its diseases have also received attention at the hands of Bauer. The suprarenals, pancreas, and generative organs have also been investigated by Bauer under various conditions. Abderhalden (31) has lately applied the dialysation test to a large number of cases, using various organs as the substrate, and his results with the ductless glands are of interest. In a healthy person the serum does not attack any gland tissue. A case of pregnancy with exophthalmic goitre was found to digest placenta, ovary, thyroid, and thymus tissue, whereas a case of exophthalmic goitre in a patient with loss of both ovaries digested thyroid and thymus only. In eclampsia, on the other hand, where marked degenerative changes are known to take place, placenta, ovary, thyroid, brain, and liver tissues were attacked. The results of all this work are of particular interest in the study of the inter-relationship of the ductless glands. We know that such a relation does exist, and work along these lines should yield most valuable information. Not only should it be possible to determine which glands are involved in a particular disease, but we may be able to base therapeutic measures upon such information. Thus in lymphatism where the thymus tissue only is broken down, treatment with pituitary extract should be beneficial, and similarly in cases of gigantism growth might be controlled by thyroid administration. The diseases of the ductless glands might possibly be solved upon these lines, and treated accordingly.

The results obtained in this particular branch of medicine weigh very largely in favour of the presence of protective ferments in the blood. It is just possible that we may detect distinctive ferments as well in such conditions.

The application of the same principle to nervous and mental diseases was due in the first place to Fauser (32), and since the publication of his work further corroboration has been forthcoming. The proteolytic powers of the serum of such patients have been tested against various antigen-like substances,

more particularly brain, testicular, and ovarian tissue.   The sera of male cases
of dementia praecox will digest testicular tissue, whereas that of a female patient
under the same conditions splits up ovarian tissue in addition to the cortical
tissue of the brain.   In cases of maniac-depressive insanity no ferments have
been detected at all, but in epilepsy brain tissue is digested.   Wegener (33) has
investigated a large number of cases and his results corroborate the findings of
Fauser.   He found a reaction with brain tissue in epilepsy immediately follow-
ing the attack.   In melancholia liver tissue, and in some cases sex glands, were
also digested.   Six cases of chorea were found to give a digestion of brain tissue,
and similar reactions were obtained in a variety of conditions, e.g. brain and
spinal tumours, meningitis, paralysis agitans.   Binswanger (34) has shown that
brain tissue was digested immediately after an attack of epilepsy, but fourteen
days after no digestion occurred.   This is very striking in view of the fact that we
find much neuroglia tissue formation in epilepsy, and the tests would suggest the
possibility of epilepsy being set up by the disintegration of brain substance.
Leri and Verpas (35) have also studied the serum reactions in epilepsy, and find
that the digestion of brain tissue is not invariable, but that the most positive
reactions were found in patients presenting most marked mental deterioration.
Again, the reaction was not found to be influenced by such factors as the number
or severity of the attacks, the age of the patient, the date of onset, or duration
of the disease.   Although advocating the fundamental principles of the Abder-
halden test they do not agree with Binswanger that the destruction of brain
tissue has any relation to the attacks, or that the test serves to distinguish
between constitutional and organic types of epilepsy.   The observations of
Kafka (36) in dementia praecox are also favourable to Fauser—the ferments
against sex glands being characteristic of this disease.   In a certain group of
cases in which the diagnosis of dementia praecox was not self-evident a number
reacted to thyroid tissue as well.   Mayer (37) found thyroid tissue, as well as
brain tissue and sex glands, was usually attacked by the serum from cases
of dementia praecox.   In general paresis he found brain tissue digested in all
cases, and sex glands and liver in five of the patients investigated.   The results
obtained by Fischer (38) are almost identical both in the case of dementia
praecox and paresis, thyroid tissue giving a positive reaction in the former
disease, where thyroid hypertrophy existed as a complication.   In functional
nervous diseases no reactions were obtained with any of the tissues used.
Bundschuk and Roemer (39) similarly report good results with brain tissue
and sex gland in dementia praecox and paresis.   The work of Theobald (40)
on dementia praecox shows the reaction to sex glands in 53 per cent. of his
cases, to brain tissue in 63 per cent., and thyroid gland in 69 per cent.   Fuchs (41)
is also convinced of the specificity of the ferments in dementia praecox, finding
digestion of the testis by the serum of males with this disease, and ovaries
by females, but never the reverse.   In contrast with these observers, who support
in general the original claims of Fauser, we have others who fail to obtain
concordant results.   Neue (42), for example, although finding the usual sex

gland characters in the serum of dementia praecox, obtained similar reactions in seven healthy males, and Oellers (43) obtained positive reactions with brain tissue in functional nervous diseases. Willige (44) in cases of paresis reports positive results not only with brain tissue, but also thyroid and testicular tissue, also a reaction to thyroid tissue only in a case with a brain tumour. On the other hand, two patients with a pituitary tumour gave a reaction to pituitary tissue, and a feeble response to thyroid tissue in one of them. Perhaps the most divergent results to those of Fauser are to be found in the work of Hauptmann and Bumke (45). They found reactions to sex gland tissue in non-mental cases as well as in normal persons, but it is interesting to note that Hauptmann confesses himself as convinced of the justification of Fauser's claims after having visited the latter in his laboratory. Brahm (46), using the polarimeter method, found that although he obtained evidence of cleavage of brain peptone in all cases of dementia praecox a similar cleavage of silk peptone occurred in about half of the cases, and he also found that the serum of these cases very frequently digested placental tissue as well. Reviewing the literature on this subject it would appear that there is some evidence of protective ferments in the blood in certain diseases of the nervous system. The most characteristic changes are met with in dementia praecox, where the sex glands appear to play a definite rôle. The disease is, however, not the only one where ferments in the serum attack sex gland tissues, since Lampe, Papazolu, and Fuchs (47) have found similar reactions to occur frequently in exophthalmic goître. The work of Abderhalden on the reactions of the serum to various organs is of interest in connexion with dementia praecox, although only three cases were tested. A male digested placenta, testicle, ovary, and brain tissue, but one who had lost both testes reacted to brain tissue only. A woman, on the other hand, reacted to ovary and brain tissue. Fauser is most emphatic in his claims for the diagnosis of dementia praecox by the ferment reactions of the blood serum, and perhaps places too much reliance upon the tests. He obtains sex gland reactions in unexpected cases, and is inclined to regard the laboratory test as superior to clinical diagnosis in such circumstances. This work upon diseases of the nervous system would appear to require much further elaboration before one can speak with any degree of finality. It has, however, served a useful purpose in pointing to the possible relationship between affections of the brain and the ductless glands. With improved technique and extended knowledge it may be possible to differentiate early cases of dementia praecox, but at present no one would be justified in condemning such a patient upon this test alone.

In the domain of infectious diseases the Abderhalden tests have been applied with apparently successful results. The question of a specific ferment in the blood capable of digesting tubercle bacilli has been approached by Abderhalden and Andryewsky (48), who report favourable results in miliary tuberculosis. Lampe (49), using tubercle bacilli, tuberculous lung, and normal lung, obtained satisfactory results in thirty cases of pulmonary tuberculosis. Jessen (50) even goes so far as to suggest that the different type of tubercle can be differentiated

by this test, and also the organ or organs involved.   Amongst other infectious diseases perhaps the most striking contribution is that of Schultz and Grote (51), who found a ferment antagonistic to lymphoid tissues in cases of scarlet fever. The interest which attaches to these observations is increased when one recalls the observations of Bernhardt in 1911 upon the transmission of scarlet fever to monkeys by the injection of lymphoid tissue from scarlet fever patients.   The serum of patients infected with typhoid, diphtheria, and anthrax bacilli, certain trypanosomes, and the Spirochaeta pallida was tested against extracts of these organisms by Voelkel (52) with negative results except in the case of typhoid. In a few syphilitic cases, however, the albumin of the Spirochaeta pallida was digested.   Syphilis does not seem to show any protective ferments, as evidenced by a large number of observations (Reines (53), &c.).   The writer, using both extracts of the Spirochaeta pallida, and also infected gland tissue, has been unable to detect any such specific ferment in the sera of infected cases.   There would appear to be a wide field for further investigation on the existence of protective ferments in the blood serum in infections by micro-organisms.   We know that the blood does exert a protective action against the invasion by micro-organisms, and that this mechanism is probably of the nature of a ferment action.   It is, of course, difficult to determine the actual specificity of such ferments, but at present such a view does not seem to be warranted by the facts at our disposal, although such a conception would help us to understand the characteristics of the various bacteria and the specific action of vaccines.   The protein or proteins in a staphylococcus may be specific for this organism, and when injected into the body excite the production of a specific ferment to destroy the staphylococcus.   The injection of streptococci, on the other hand, would presumably have no effect on the growth and development of the staphylococci already present.   There are, however, a number of cases on record where a vaccine of a different organism has been given with satisfactory results. Further, the antitryptic powers of a given serum are found to be diminished in general bacterial infections, and it is quite possible that the destruction of these organisms is brought about by the non-specific ferments in the blood.

The above review of the work which has been done in the application of the Abderhalden test in the field of general medicine, extensive though it has already become, would not be complete unless reference were made to some of the more remote instances.   Thus attempts have been made to ascertain the nature of infection with various intestinal parasites in man and animals by the serum test (Rubinstein and Julien (54)).   Gebb (55) has applied the test to various diseases of the eye, and skin affections have also received attention at the hands of Jarisch, Rübsamen, Reines, and Bauer.   The latter author has also reported results with the blood proteins in pernicious anaemia, and with muscle proteins in diseases of the muscular system.   Kabanow (56), using preparations from various segments of the alimentary tract, professes to be able to diagnose the special organ involved in a variety of gastro-intestinal diseases.   The application of the tests to animals has been attempted by

numerous observers, particularly Abderhalden, McCord (57), Falk (58), Schlim-
pert and Issel (59), Naumann (60), Schwarz (61) (cows), and Schattke (62) (cows).

The foregoing account would therefore indicate that the application of the
Abderhalden tests is unlimited.   By this means we may learn more concerning
the inter-relationship of the ductless glands and the part these organs play
in disease.   The discovery of the occurrence of such protective ferments in
the blood is of the greatest practical importance to clinical medicine, not so
much, perhaps, from the point of view of diagnosis, but rather as a means
of linking up our knowledge, and placing many points upon a definite scientific
basis.   The whole question has created a profound impression throughout the
scientific world, and has been the means of stimulating a large body of workers
to investigations along entirely new lines.

The Specificity of the so-called Protective Ferments, and the Nature of their Action.

The above brief summary will, I hope, serve to demonstrate the possible
occurrence of such protective ferments and further their alleged special
characteristic, namely, specificity.   It will also tend to show that the protein part
of the organ is attacked, thus limiting the question of specificity to the proteins
themselves.   Now Abderhalden claims specificity for every type of protein, and
explains this in the following way : All the proteins when hydrolysed give
practically the same final products, namely, amino-acids, to the number of some
twenty or more.   Now, when we come to synthesize these twenty amino-acids
into a protein complex by simply altering the sequence we can obtain billions of
different proteins, 2,432,902,008,176,640,000 in fact, without in any way altering
the form of combination.   It is quite possible that one protein does not occur
alone in a single cell; on the other hand, there may be several proteins present
grouped together in a particular way.   Thus we see the number of protein
combinations is infinite, and no one can conceive, much less calculate, the actual
numbers.   In this question chemical physiology soars into realms even
transcending those of the astronomer.   Thus we can easily understand that there
is a specific protein or group of proteins in a chorionic villus cell, in a carcinoma
cell, and a tubercle bacillus, to quote a few instances.   These various ferments
which have been shown to develop in the blood are regarded by Abderhalden as
products of the leucocytes, a view first suggested by Sajous in 1903.   Recently
he has modified this view and now suggests that the protective ferments are
generated in the organ involved and present there originally.   Their passage into
the blood-stream under the influence of morbid conditions may thus be a specific
anomaly.   No matter what their real origin, one point stands out pre-eminently,
and that is their rapidity of formation and just as rapid disappearance.   The fact
that they are so short-lived would suggest that they are not of the nature of
antibodies, and would also explain why we have no evidence of specific anti-

ferments. Needless to say the acceptance of such a simple and sweeping theory of the nature of immune bodies has not received general acceptance, and it has been attacked mainly from the experimental point of view. Now Abderhalden replies to many of his critics by assuming that their methods are at fault, and states that trustworthy results can only be obtained by one who is thoroughly familiar with the method and knows the sources of error. He points out that the chief sources of error are to be found in defective dialysing tubes, and in the preparation of the organ extracts. Although it may be true that some sceptics have failed in one or other of these particulars, it is only too apparent that these fallacies cannot be used to condemn every mistake in diagnosis. With regard to the first source of error, Abderhalden has attempted to obviate this by separating the protein substances actually digested by coagulation and ultra-filtration. The work of Michaelis and Lagermarck (63) is of interest in this connexion, as they suggested the use of colloidal ferric hydroxide, and at the same time vigorously attacked the theory upon their own results. The second source of error is said to be due to the presence of traces of blood in the tissue extracts, also to blood-vessels and connective tissue, all of which will undergo digestion by specific ferments in the blood against blood constituents. It is quite true that if the blood is removed from the organ extract abnormal reactions do not occur, but the other objections are quite unfounded, as an absolutely uniform placental tissue is unknown. The chief efforts of Abderhalden since the inception of the tests have been mainly devoted to polemical literature, and the reader and experimental worker in this field is left in doubt whether any one but Abderhalden and his co-workers can possibly carry out this simple test. In the dialysation test, depending as it does upon the liberation and diffusion of peptones and amino-acids by the action of the ferment on the tissue applied, it was thought possible to estimate the nitrogenous constituents of the dialysate, and so place the test on a quantitative basis. Abderhalden (64) and also Griesbach (65) have published a number of estimations, and the differences, though slight, appear to confirm the ninhydrin test. The work of van Slyke and others (66), carried out with the most approved technique, tends to show that no such differences exist, and consequently they consider the results should be viewed with caution. The use of coloured substances has also been advocated as a means of detecting the ferments, but with little success. Oeller and Stephan (67) have shown how better controls can be made, but they conclude that the method cannot be applied for clinical diagnosis until the theory of protective ferments is established on a sounder basis. That the theory is still open to many objections is obvious from the ever-increasing volume of literature on the subject. On the one side we have the claims of Abderhalden and his co-workers endeavouring to prove by abundant experimental data the reliability of the theory, and on the other equally eminent workers who fail to obtain such consistent results. Abderhalden (68) states that he has carried out over six hundred pregnancy tests alone, using both the optical and dialysation methods, with only one or two errors. He has also published observations on the production of specific ferments after the

introduction of a variety of protein bodies into the blood-stream.   With various co-workers, especially Schiff (69), he has attempted to prove the specificity of intracellular enzymes for their own particular tissues.   Fuchs (70) also believes in the absolute specificity of the protective ferments, and has shown that rabbits treated with human kidney tissue yielded a serum ferment which was capable of digesting kidney tissue, and kidney tissue only, in eighty-eight hours.   The abundance and variety of the observations carried out on these lines render it impossible to review them all, but the above instances may serve to show the chief points advocated by Abderhalden and his supporters.   In contrast to the excellent results obtained by Abderhalden and Schiff with intracellular enzymes we have the experimental work by Pincussohn and Petow (71).   They found that the normal serum of an animal can split up the peptone prepared from its own muscle tissue or that of an allied species, but has no such action on the muscle peptone of a foreign species.   Such results cause one to pause, and particularly so when the actual observations appear from the figures to be more conclusive than those obtained by Abderhalden with the same technique.   Is it possible that this explains why human placental tissue is broken down by pregnant human serum simply because it is derived from a human being, and not from another animal?   The explanation of this apparent discrepancy will be more evident after we have discussed the mechanism of this ferment action.   Singer (72) goes so far as to deny the specificity of the ferments produced by the parenteral introduction of protein substances upon the basis of his experimental work in animals and man.   After the production of haematoma, or injection of serum albumin, he found ferments in the blood capable of digesting liver, muscle, and placental tissue.   On these grounds he explains the occurrence of positive reactions with placental tissue in sera obtained during menstruation, as recorded by some writers.

The Mechanism of the Action of the so-called Protective Ferments.

The observations of numerous workers who have failed to establish the specificity of the ferments, particularly those of Schäfer (73), Oeller and Stephan, Michaelis and Lagermarck, Leitch and Bulloch, are sufficient to show that other factors apart from any purely technical errors are responsible for the divergent and non-specific results.   Whether we regard these ferments as specific or not, practically all observers are agreed that proteolytic ferments are to be found in increased amounts under certain conditions.

In my own work I have found that the injection of freshly extracted placental tissue will give rise to a ferment in the blood capable of digesting placental tissue from the same source.   If now this placental extract is heated to 60° C. for half an hour and then injected, no such ferment can be detected in the blood-stream.   This apparently crucial experiment Abderhalden neglected to perform, and in consequence it would seem that his theory requires considerable modification.   The ferment is found in the placental tissue itself, and as such is injected

into the animal. Now this would explain the rapidity of appearance of the ferment in question, its sudden disappearance, and in consequence the absence of any antiferment formation. It would also explain many points which have been observed in the application of the tests to clinical diagnosis. For example, a morbid degeneration of any organ would probably lead to an excessive formation of autolytic ferment in this organ, with the escape of this ferment into the blood-stream. The regularity of occurrence and relatively large quantities of ferment present in the serum during the later stages of pregnancy would thus receive explanation. Similarly, in exophthalmic goitre, the ferment liberated would be capable of digesting exophthalmic goitre tissue, and not necessarily normal thyroid tissue. Heilner and Petri (74) and de Waele (75) have noticed the rapidity of formation of the ferments, the interval being regarded by them as quite insufficient for the production of specific ferments. The introduction of a foreign protein may therefore simply serve to activate the preformed ferments in the blood, a view which seems to be supported by recent experimental data. de Waele found that any alteration in the physical condition of the serum globulin gives rise to an intense Abderhalden reaction, and it appeared probable that, like the precipitin reaction, the process was a purely physical one. A similar physical globulinolysis has been advocated by McDonagh (76) to explain this reaction. The influence of various physical alterations of the serum has been clearly demonstrated by Plaut (77). He points out an entirely new source of error in the Abderhalden reaction, showing that portions of organs added to serum absorb and retain certain constituents. As a result of this physical and non-specific absorption an increase or diminution of dialysable substances occurs, which leads to entirely erroneous results. With serum from guinea-pigs and human serum he obtained positive reactions with placental tissue, kaolin, talcum, starch, barium sulphate, silicates, chloroform, &c. He concludes that the placental tissue in Abderhalden's test merely acts as a mechanical absorbent. Peiper (78), Friedmann and Schönfeld (79), and Bronfenbrenner (80) have reported identical results, and the work of these authors has been entirely corroborated by the writer of this review. The work of Flatow (81) and Herzfeld (82), while demonstrating that specific results can be obtained, also points to the influence of the organ extract as a mechanical absorbent of some fundamental constituent of the reacting serum. Following this absorption, ferments, whether specific or not, carry out the hydrolysis of protein materials. The study of the mechanism of the Abderhalden reaction on these lines has been considerably advanced by Jobling and Petersen (83). The digestive power of the serum is said to be dependent on the normal proteolytic ferments, their action being held in check by an antiferment under ordinary conditions. Since this antiferment can be removed from the serum either by lipoidal solvents, or the various mechanical absorbents used by Plaut, we have an explanation of the occurrence of non-specific results in either a positive or a negative sense. As the digestive powers of the serum are increased by such treatment, it would tend to show that the serum protein is itself attacked and not the boiled tissue as used

in the Abderhalden test. A similar view has been advanced by Bronfenbrenner (84), who regards the Abderhalden test as specific, since the reaction develops simultaneously with antibodies during the process of immunization.   The sensitized substrate or organ extract removes the antitrypsin from the serum, autodigestion of the serum then proceeds with dialysation of the products, and a positive reaction.   All the observations recorded above tend to show that the so-called protective ferments do not exist in the sense assigned by Abderhalden, and my own work supports these conclusions. The reaction depends upon an increase of the normal and general proteolytic ferments, as can be readily shown by polarimeter determinations. By shaking serum from pregnant and non-pregnant women with barium sulphate, and observing the digestive capacity of such sera towards placental peptone in a polarimeter, certain points can be ascertained. The amount of rotation observed in the pregnant serum is generally ten times as great as that usually obtained with the Abderhalden method, the normal serum giving readings which would be regarded by Abderhalden as a positive diagnosis of pregnancy.   The influence of barium sulphate on normal human serum has also been studied, and the results point to digestion of the serum proteins by the non-specific proteolytic ferments normally present.   The earlier observations pointed to the possibility that the barium sulphate method would be generally applicable, and that it probably activated the specific ferment in the serum, since normal sera behave in exactly the same way.   I am inclined to agree with the authors quoted above.   Jobling and Petersen believe that the antiferment is related to the unsaturated fatty acids of the serum, since it is removed by lipoidal solvents or by mechanical absorbents. The serum ferments, being now freed from the antiferment, are able to act upon the serum proteins and not upon the actual tissue or organ extract added.   This conclusion is in accord with practically all recent developments, and would explain many of the discrepancies met with in the Abderhalden method as applied to clinical diagnosis. Kolmer and Williams (85) are of the opinion that both normal and non-specific, and also specific, ferments are present in pregnancy serum.   The former are released through absorption of the antiferment by means of various non-specific organic and inorganic substances, while the latter are only set free when the antiferments are absorbed by the specific protein antigen.   This statement, based upon a number of experiments, is again supported by the polarimeter observations recorded by the writer.   The object of new methods should therefore be directed to removing the non-specific ferments, as in the dialysation method these may lead to occasional errors in diagnosis.   With the use of the polarimeter test this source of error can be eliminated by making the test a purely quantitative one.   There seems to be little doubt that the specific ferments do act upon the tissue matrix as well as upon the serum proteins, as otherwise we should not find such wide variations in the polarimeter readings.   The degree of protein digestion is also found to be much greater when tissues or organs are used than when various inorganic substances are substituted.   An interesting feature observed by Kolmer and Williams was the opalescent or milky appearance of the pregnancy sera when incubated with

placental tissue.   This change was not so marked when other tissues were used, and almost totally absent when inorganic absorbents were substituted.   We appear, therefore, to be dealing with a variety of ferments which exist preformed in the serum, some of which are specific, whilst others are non-specific.   The whole subject requires more thorough investigation before one can draw any definite conclusions from these experiments.

Are the Protective Ferments related in any way to the Amboceptors of Ehrlich's Side-chain Theory?

Steising (86) claims to have separated the ferment responsible for the Abderhalden reaction into an amboceptor and complement.   He inactivates the pregnancy serum by heating to 58° C. for an hour, and then reactivates it as desired by the addition of fresh male serum.   He investigated in this way the sera of ten pregnant women with satisfactory results, and on this basis regards the technique as generally applicable to a large number of pathological conditions.   Similar results have been recorded by Stephan (87), Hauptmann (88), Bettencourt and Menezes (89), using a variety of sera as complement.   Williams and Pearce (90) found, on the other hand, that inactivation of the serum, although diminishing its action, did not entirely destroy the protective ferment.   Abderhalden has also shown that the addition of complement has an effect upon the reaction, but is not inclined to accept the side-chain theory of Ehrlich as an explanation of its action.   We know from the work of Jobling, Eggstein, and Petersen (91) that the normal proteolytic ferments of the serum are much more resistant to heat than the serum complement, and it is suggested therefore that the results recorded above are simply due to the addition of fresh ferment to the inactivated serum.   This explanation in the light of the experimental results recorded in a preceding paragraph seems more than probable, and thus removes the reaction from the realm of the side-chain theory.

The Relation of the Abderhalden Reaction to the Phenomenon of Anaphylaxis.

The high degree of specificity of anaphylactic reactions would appear to have some relation to the same specificity claimed for the Abderhalden reaction, more especially as we are dealing with foreign proteins in both cases.   The tendency of all observations on the production of anaphylaxis has been to show that it is the breakdown products of the protein liberated in the body which exert the poisonous action, and these have been designated anaphylatoxins.   The work of Wheeler and Vaughan (92) is of especial interest in this connexion as they produced a similar condition to anaphylaxis by digesting various proteins with alcoholic sodium hydroxide.   Kolmer and Williams have shown that the ferments in the Abderhalden test are capable of giving rise to digestion products

which exert anaphylactic reactions similar to those obtained by Wheeler and Vaughan. They conclude that the Abderhalden reaction is probably anaphylactic in nature in so far as its mechanism is concerned, and assume that specific ferments exist and exert a digestive action upon the tissue to which they are directed. It is no doubt perfectly true that the proteolytic ferments in the blood do play a part in the phenomena of anaphylaxis, but they cannot be invoked to explain many of the reactions which occur in this condition of hypersensitivity. By this hypersensitivity we mean the property an animal possesses of reacting with certain typical symptoms to a second injection of the same material as was used in the first injection. These symptoms, especially cramp in various muscles and a sudden fall of temperature, follow almost immediately upon the second injection. This production of anaphylactic shock is so rapid—in some cases only a few seconds elapse—as completely to rule out any ferment action. Further, we know that the proteolytic ferments present in the serum are capable of exerting their action during the time when a second injection of the foreign protein does not produce any anaphylactic reaction. Another important point is the necessity of using the same protein to produce the shock as was used to render the animal hypersensitive. It is clear, therefore, that whatever part, if any, the protective ferments play in anaphylactic reactions their action is uncertain, and factors other than those purely chemical in nature must play a prominent part. The sudden appearance of anaphylactic shock tempts one to suggest that physical changes, e. g. osmosis, hydrogen ion concentration, and electrolytic dissociation in the blood, play a large part in its production. The work that has been published up to date dealing with this problem is unfortunately far from convincing. The conclusions are based upon scanty experimental evidence, in many cases only one or two animals being used. The study of a problem of this nature, which is absolutely fundamental, involves much labour, and the solution is not so simple as some writers would lead us to believe.

Summary and Conclusions.

The above review of the observations made upon the Abderhalden tests, though admittedly incomplete, will serve to show that the theory has excited widespread interest. Contributions on all phases of the subject have appeared in the medical and scientific journals of nearly every country in the world. Since the views of Abderhalden were first made known the application of the method has undergone a rapid extension in many directions. Recent work has, however, tended to show that the principles of the method as laid down by Abderhalden do not coincide with the experimental data, and consequently other explanations must be offered. Like many of the modern pathological methods, it was claimed at first to be quite infallible, and not only made diagnosis in a test-tube absolutely certain, but also laid bare many of the problems of immunity which had hitherto remained concealed. The history of pathology and pathological methods illustrates

how often tests introduced to diagnose one or more diseases have failed in actual practice to attain the high standard advocated by their originator. The introduction of the Abderhalden tests as an exact method of diagnosis before the fundamental principles on which they were based had been conclusively proved merely adds another page to our history of failures. That the work has, however, been of value from a scientific point of view cannot be denied, and it is to be regretted that this side of the problem was neglected in favour of the more sensational work on serological diagnosis. The whole theory of Abderhalden touches the root of the problem of immunity, namely, the cell itself, and also emphasizes the fundamental importance of the protein constituents of the cell. In this alone the work has made a great advance in our conception of immunity, and answered many questions on a purely chemical basis. The advances in our knowledge of colloidal chemistry and ferment action may thus be brought into line, and many problems of physiology and clinical medicine await solution by this means. In the near future it may be possible in the light of new knowledge so to modify the Abderhalden tests as to give them a far greater value, not only in the study of pathological changes associated with morbid conditions, but also as aids to clinical diagnosis.

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AN EXPERIMENTAL INVESTIGATION ON DIARRHOEA AND VOMITING OF CHILDREN [1]

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Synopsis.

I. *The Object and Basis of the Research.*

THE following is a preliminary account of experiments undertaken in order to elucidate the condition of diarrhoea and vomiting of children. From a bacteriological point of view, this pathological condition has been extensively

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[1] Giving results of an investigation subsidized by the Local Government Board.

investigated ; one has but to recall the association of diarrhoea and vomiting by various workers with the Bacillus enteritidis sporogenes, streptococci, Morgan's bacillus, Shiga's bacillus, and many others, to realize this.   Much work has also been done on the bacteriology of milk, in order to demonstrate a relationship between diarrhoea and vomiting of children and infected milk.   In consequence of the marked difference in the structure and properties of the bacilli isolated in different epidemics, it has been thought probable that, after all, there may be no specific bacillus responsible for the disease, and that, with increasing knowledge of the chemistry of the alimentary tract, there was room for an attack on this important subject along lines different from those which have already gained so much attention.   My own work here described is, therefore, an account of an investigation undertaken along chemical lines, and this paper treats only of experiments dealing with the behaviour of animals when under the influence of a toxic substance normally present in the alimentary tract.   (In a later paper, I shall describe the effects of the treatment of children suffering from diarrhoea and vomiting, the treatment following along lines indicated by this experimental work.)   I do not propose in this paper to discuss the many important researches carried out by other workers on this disease along bacteriological and other lines not germane to the present investigation.

In the first place it may be well to state certain fundamental facts which bear upon this work.

Some years ago, an extremely active and toxic substance was isolated by Barger and Dale (1) from ergot.   This substance is known as β-imidazolyl-ethylamine (which throughout this paper will be called β-i).   The formula of this substance makes it clear that it is derived from histidin by the simple removal of carbon dioxide thus :

$$\underset{\text{histidin (harmless)}}{\overset{\text{NH}-\text{CH}}{\underset{\text{CH}=\text{N}}{\Big|}}\!\!>\!\!\text{C}\cdot\text{CH}_2\text{CHNH}_2\text{COOH}-\text{CO}_2} = \underset{\beta\text{-i (toxic)}}{\overset{\text{NH}-\text{CH}}{\underset{\text{CH}=\text{N}}{\Big|}}\!\!>\!\!\text{C}\cdot\text{CH}_2\text{CH}_2\text{NH}_2}$$
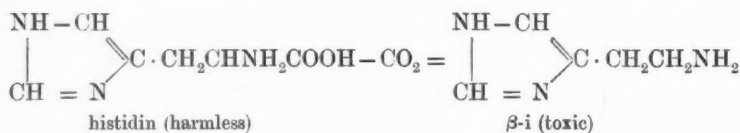
Other substances, less active physiologically, now known as tyramine and isoamylamine were also obtained from ergot by the same workers, and the chemical constitution of the substances indicates that they are derived from tyrosin and leucin respectively, in a similar way to that by which β-i is derived from histidin.

The next interesting discovery was also made by Barger and Dale (2) when they demonstrated the presence of β-i in the alimentary canal of normal herbivora.   They were led to investigate this point by the well-known fact that a watery extract of the mucous membrane of the intestine has a marked depressant action on the blood-pressure, and in other ways has physiological effects similar to those produced by β-i.

It is interesting to note that β-i may be placed in the same category as

other ptomaines whose names are so familiar, viz. cadaverin and putrescin. The formulae of the two substances are:

$$NH_2 \cdot CH_2CH_2CH_2CH_2CH_2NH_2 \quad \text{cadaverin,}$$
$$NH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot NH_2 \quad \text{putrescin.}$$
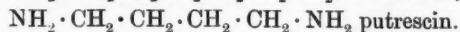
Their formulae show them to bear a close relation to lysin and the diamino-valerianic acid portion of arginin respectively. The similarity of formation of all these ptomaines can thus be seen:

$$COOHNH_2CHCH_2CH_2CH_2CHNH_2COOH - 2\ CO_2$$
lysin

$$= NH_2CH_2CH_2CH_2CH_2CH_2NH_2$$
cadaverin

$$COOHNH_2CHCH_2CH_2CHNH_2COOH - 2\ CO_2 = NH_2CH_2CH_2CH_2CH_2NH_2$$
diamino-valerianic acid   putrescin
(from arginin)
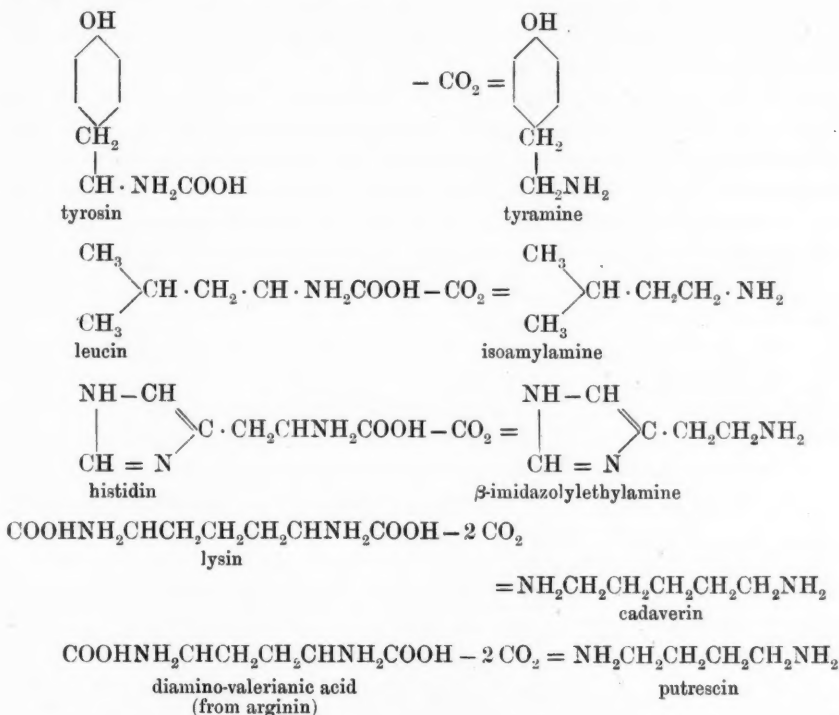
The change from lysin and diamino-valerianic acid to cadaverin and putrescin was shown by Ellinger (3) to be the result of anaerobic bacterial decomposition. Similarly, Akermann (4) was able to produce β-i from histidin. Twort and I (5) have published a method for the isolation of bacilli capable of converting histidin into β-i. This bacillus was isolated from the contents of the intestine of human beings and other animals. The difference between the results of Ellinger and ourselves is that the removal of CO_2 from histidin does not at all depend on the presence of oxygen and goes on aerobically and anaerobically, while Ellinger's results depended on anaerobic conditions. The difference is probably to be explained by the fact that Ellinger carried out his experiments with a very mixed growth, which aerobically destroyed the amines as they were formed, while we worked with a single strain of bacillus, and so had

no such complicating factors. We did find, however, that one important factor influenced the change, namely, the presence of acid. In an acid medium, or what comes to the same thing, in the presence of carbohydrate—for bacteria always produce acid if sugar is present—the end product of the bacterial action on histidin was quite inactive physiologically, and certainly was not β-i.

While putrescin and cadaverin have been mentioned in order to show the analogous position they hold as compared with β-i, and that this last substance can also be classified in the ptomaine group, it is necessary to add that cadaverin and putrescin are, compared to β-i, almost inactive substances. It is, in fact, impossible to suppose that symptoms of vomiting and diarrhoea can, in any case, be ascribed to them.

In the case of β-i, however, it is different. This substance has an extraordinary power of stimulating unstriped muscle, including that of the alimentary canal, bronchioles, and uterus. If given by mouth to a cat, it immediately causes vomiting and diarrhoea. The amount of diarrhoea is of course proportional to the amount of β-i that escapes being thrown out of the stomach in vomiting.

Here, then, we have a substance present in the mucous membrane of the alimentary canal, whose constant formation, at least in the lower end of the intestine, is almost certain because of the presence of the amino-acid histidine and the necessary bacteria; a substance of very potent physiological activities, capable of producing diarrhoea and vomiting. With this knowledge, it seemed to me that, in view of the failure of previous research to associate diarrhoea and vomiting with any causal factor, either bacterial or chemical, it was important to test the hypothesis that β-i is either the substance, or one of the substances, which plays an important part in the production of such symptoms. Various hypotheses involving β-i as the cause of such symptoms can be formulated:

1. That in diarrhoea and vomiting there is excessive production of β-i in the intestine due either to:

   (a) A changed or increased bacterial flora;

   (b) A changed chemical or physical condition which prevents the absorption of histidine of the food and allows a subsequent increased production of β-i; or to

   (c) A changed condition which allows bacteria acting on histidin to produce a relatively large amount of β-i rather than innocuous products (such an innocuous product might be β-imidazolylacetic acid).

2. That in diarrhoea and vomiting there may or may not be an increase of β-i, but the β-i, present in the alimentary canal and mucous membrane, becomes active in some way, and is absorbed into the blood-stream at a time when the animal is incapable of resisting its toxic action and rendering it innocuous.

The experimental portion of this work has therefore been carried out on the assumption that β-i is one of the most important factors in epidemic diarrhoea and vomiting (I do not wish to imply it is the only one). Work has been done to discover the conditions under which it is absorbed from the intestine,

the conditions which prevent its absorption, the conditions which allow of its rapid decomposition after absorption into the blood-stream, and, on the other hand, the conditions which allow it to have its full toxic action on the animal.

Even if further research should show that β-i is not the important chemical agency at work in this condition, it is felt that many of the facts to be described will apply equally to other toxic substances and that the immunity against and liability to suffer the full toxic action of physiological substances, as met with in the animal body, follow general rules.

The problem is then resolved into two parts : (1) How to diminish or prevent the absorption of toxic substances from the intestine while at the same time interfering with other physiological activities as little as possible. (2) How to raise the immunity against such toxic substances as are absorbed.

In the experimental work to be described, the former of these problems has taken up the most time. At first this appeared to be the more important, and it is certainly the easier problem to be worked at. As the work progressed, however, it must be confessed that the second part impressed itself more and more upon me, and, although definite results were obtained along these lines, there remain many points to be cleared up. I feel confident that a solution of the problem as to the different powers of resistance to a toxic substance, possessed by animals under varying conditions, is most vital, not only from the point of view of epidemic diarrhoea and vomiting, but also in the case of all conditions of toxaemia. Why a small quantity of toxic substance should in one animal cause fall of blood-pressure, paralysis of the respiratory centre, and death, and in a second animal of the same type leave the animal practically untouched, seems to me to be the crux of a great number of pathological conditions.

In my opinion, the reasons for which I will give later, a child suffering from diarrhoea and vomiting is in a condition for experiencing the full effect of a toxic substance, so that the absorption into the blood-stream of a small quantity of β-i is capable of producing the full toxic action, while in a normal child a similar quantity would leave the child untouched.

The reasons, therefore, why β-i was chosen as a suitable substance in the following experimental work, and why, also, it is considered an important factor in diarrhoea and vomiting of children, are as follows :

1. β-i is present in the intestinal mucous membrane of normal animals (Barger and Dale).

2. Bacilli have been isolated from the intestine capable of producing β-i from histidin; also from meat extract, in this latter case from carnosin (histidyl-alanin) (Twort and Mellanby).

3. β-i is a toxic substance (6) capable of causing—

(a) Diarrhoea and vomiting,

(b) Fall of systemic blood pressure,

(c) Depression of the respiratory centre,

(d) Coma,

that is, symptoms met with in diarrhoea and vomiting of children.

II. *Experimental Procedure.*

For the animal experiments in this work the cat was used. Various anaesthetics were employed, and, as will be seen later, with markedly differing results. In many of the earlier experiments, urethane was injected about an hour before the experiments were started, 1 to $1\frac{1}{2}$ grm. per kilo of body-weight being used. This, together with a little ether or chloroform or A. C. E. at the beginning of the operative procedure, sufficed to keep the animal anaesthetized for as long as required. In the later experiments, for reasons which will be explained, urethane was discarded in most cases, and chloroform only or A. C. E. was used. After anaesthetizing the animal, tracheotomy was performed, and in most experiments the blood-pressure in the carotid artery recorded. The abdomen was next opened, the large omentum moved back, and loops of gut measured. Lengths (25 cm.) were tied off after the method of Moreau. The region chosen for the loops varied with the experiment. In preparing these, it was necessary to keep the blood-supply and lymphatics as normal as possible, and further not to expose the intestines for longer than could be helped. A measured solution, usually 5 c.c., of β-i of a known strength was then injected into the loops. If the effect of drugs was sought in the experiment, the drug to be tried was injected into the intestine prior to the β-i. The intestines were then carefully replaced in the abdominal cavity so as to avoid twisting of the mesentery, and the abdominal cavity closed up. The animal was then left for a specified time. At the end of this time, the loops of the intestine were removed, opened up and washed out carefully, so as to bring the volume of the washings up to 300 c.c. This was then boiled, and the β-i *not* absorbed during the experiment estimated. To estimate the β-i, it was not possible, with the small quantities used, to find a chemical method. A biological method was therefore employed. This method was one used by Kehrer (7), and consisted of suspending one horn of the uterus of a guinea-pig in oxygenated Ringer solution, and finding the smallest quantity of solution capable of causing a full contraction of the uterus. This quantity was compared with the amount of the original β-i solution capable of causing a full contraction, from which data it could be easily calculated how much β-i had disappeared from the loop during the experiment. If, for instance, it took 0·3 c.c. of the original solution, and 0·6 c.c. of solution after being in the intestine, to bring about the same change in the guinea-pig's uterus, it can be readily seen that 50 per cent. of the β-i originally used must have been absorbed.

The advantages of the method are :

1. It is fairly rapid with a suitable uterus.

2. It is very delicate and is therefore suitable for small quantities of β-i.

The disadvantages of the method are :

1. Every uterus varies in susceptibility, so that the contents of all loops of intestine together with the control in each experiment must be tested on the same uterus.

2. The uterus varies in irritability during the experiment, and this can only be eliminated by repeated trials.

3. The method varies in accuracy of results at different times, and can never be as good as a reliable chemical method.

In spite of the obvious disadvantages, good relative results can be obtained by taking care that such conditions as temperature, constitution of Ringer solution, and times of injecting the drug are kept constant.

In the majority of cases two cats were experimented on, one being a control animal. For a long time, until something was learned as to the susceptibility of the animals to β-i and the conditions which regulated such susceptibility, very great difficulty was experienced in making the experiments comparable and successful. On account of the differences between animals, it can be readily understood that each experiment has to be repeated several times before any result can be accepted, and the animals have to be obtained in similar conditions for similar experiments. For instance, it is useless to test the absorptive capacities in cats, one of which had been fed on milk and the other on meat. In all experiments, except where other points were being tested, the cats were kept without food for twenty-four hours prior to the experiment, so that the small intestine was clear of food when required. Except in one or two cases where it is otherwise stated, it can be assumed that several experiments were made to prove a given point, although details of all such experiments are not given in the protocols.

III.   *Preliminary Experiments.*

(a) *The disappearance of β-i from the small intestine during the time of the experiment depends only on absorption.*

In experiments to test this point the blood-vessels in the mesentery supplying loops of 25 cm. of intestine were tied before the β-i was injected. The animals were then left for varying periods of time and the amount of β-i remaining in the intestine was compared with the original β-i solution injected. No β-i could be absorbed in such a case, and if there was any deficiency in the β-i after its sojourn in a loop of intestine, this must have been brought about by bacterial decomposition. In Experiment 71 the β-i solution remained in the intestine for two hours and five minutes, after which the cat was killed. It will be seen that there was no loss of β-i in this time.

Inference: There is no disappearance of β-i from the small intestine when the mesentery is ligatured.

(b) *The independence of the absorption of β-i in each loop of the intestine.*

The number of instances in which the activity of one part of the alimentary canal depends upon that of another part might lead one to expect that absorption from one loop of the intestine would be influenced by the condition of the

proximal loops.   Without going so far as to deny some interdependence between neighbouring parts of the intestine, it is clear that cutting off the blood supply above the experimental loop does not do away with the absorbing power of that loop.

In Experiments 71 and 73 the mesenteric vessels supplying loops of intestine 25 cm. in length were tied at various parts of the alimentary canal.   It will be seen that this interference with the blood supply did not prevent 70, 47, 55, 44, and 50 per cent. of the β-i injected disappearing respectively from other loops of small intestine with the blood supply intact.

Inference: The absorption of β-i is not affected by tying the blood-vessels of a part of the intestine other than that in which the β-i is placed.

(c) *The increasing rate of absorption in passing from the duodeno-jejunal flexure to the caecum.*

The absorption of β-i from the small intestine increases from the duodeno-jejunal flexure to the caecum.   The difference in the rate of absorption between the extreme ends of this part of the small intestine is marked, but becomes less so as the loops approach one another.

In Experiment 52 it will be seen that 59 and 60 per cent. of the injected β-i were absorbed from loops of intestine at the duodeno-jejunal flexure, whereas 84 and 89 per cent. disappeared from similar loops at the caecal end of the small intestine in the same time.

The maximum rate of absorption is always attained at the lower end of the small intestine.

In Experiment 134 the loops of intestine in each cat are placed nearer to each other.   Loops A_2 and B_2 were at the caecal end of the small intestine, and loops A_1 and B_1 25 cm. distance higher up than A_2 and B_2.   In the time allowed for absorption, viz. 1 hour 18 minutes, 50 and 55 per cent. of the injected β-i disappeared from A_1 and B_1 and 55 and 66 per cent from the lower-placed loops A_2 and B_2.

Inference: The nearer the caecum, the greater is the absorptive capacity of the small intestine.

IV.   *The Effect of Food-stuffs and Bile on the Rate of Absorption of* β-i *from the Small Intestine.*

In this place I wish only to refer to the effect of feeding on the rate of absorption of β-i in the small intestine.   Later, it will be seen that feeding of some food-stuffs has also an important effect on the resistance offered by the animal to the β-i after absorption.

(a) *The effect of milk.*

If milk is given to a cat some hours prior to the injection of β-i, then the rate of absorption of the β-i from the intestine is diminished.

For instance, in Experiment 123, 100 c.c. of milk were given to a cat 4 hours 30 minutes before the β-i was injected. In this cat, 50 per cent. of the β-i was absorbed in two hours, while in the control cat 66 per cent. was absorbed.

Experiment 37 shows a similar result.

Milk, therefore, depresses the absorption of β-i from the intestine.

(b) *The effect of meat.*

A cat digesting and absorbing meat also absorbs β-i at a slower rate than a non-digesting cat.

This fact is seen in Experiments 125 and 129.

In Experiment 125, 30 grm. of meat (without fat) were eaten 1 hour 50 minutes before the β-i was injected. During the time of intestinal absorption, 1 hour 30 minutes, the meat-fed cat absorbed 36 per cent. of the injected β-i, against 46 per cent. in the control non-digesting cat.

In Experiment 129 the meat was eaten $4\frac{1}{2}$ hours before the injection of β-i into the intestine. The time of absorption allowed was $2\frac{1}{2}$ hours. The meat-digesting cat absorbed 70 per cent. of the β-i, and the control cat 75 per cent. This difference is small, but the time allowed for absorption was long, $2\frac{1}{2}$ hours, and this length of time always tends to nullify effects, because of the natural slowing in the rate of absorption that takes place in such experiments as these. Consequently, in course of time, the amounts of β-i remaining unabsorbed in all loops tend to approximate closely.

During the digestion of meat the rate of absorption of β-i from the intestine is diminished.

(c) *The effect of fat.*

Fat is known to have such a marked inhibitory action on intestinal functions that it might be expected that it would have an inhibitory action on the absorption of toxic and other substances. For instance, fat depresses the movements of the stomach and alimentary tract, and also inhibits the secretion of gastric, and therefore of pancreatic, juices.

The experimental work here described demonstrates that fat also depresses the absorption of β-i from the intestine, but the effect is not so marked as one might expect.

In Experiment 145, 20 grm. of fat were eaten by cat A six hours before the β-i was injected into the intestine. In one hour, 36 per cent. and 30 per cent. of the β-i were absorbed in cat A, while in the control non-digesting cat B 42 per cent. and 42 per cent. disappeared from corresponding loops of intestine. Similar results were obtained in other fat-feeding experiments quoted in protocols.

The question now arose as to whether the inhibitory action of fat on absorption was due to a local effect on the absorbing portion of intestine, or whether it was due to some previous action in its passage along the intestine,

in which latter case the action might be considered indirect. In order to test whether the fat action was direct or indirect, other experiments were performed in which olive-oil emulsion was placed directly into the loops of intestine before injecting β-i solution into the same loops.

Experiments 144 *a* and 144 *b* demonstrate that fat placed directly into the intestine has as large an inhibitory action as when the fat is eaten. In these experiments it is seen that 60 per cent. and 60 per cent. of the β-i are absorbed from the loops also containing olive oil, while the control loops without fat absorb 81·6 per cent. and 70 per cent. of the β-i respectively. It is probable therefore that the inhibitory action of fat on absorption is a local and direct one.

Inference :

1. The absorption of β-i from the small intestine is slightly delayed if the animal is previously fed on fat.

2. This action of fat is a direct one on the epithelium of the absorbing portion of intestine.

(*d*) *The effect of carbohydrate.*

The result of this portion of the work is not clear, for the direct feeding of pure carbohydrate to cats before the injection of β-i into the intestine was not tried. Instead of this, a solution of dextrose was injected into the intestine, and in all the experiments performed there was a marked diminution in the rate of absorption of the β-i. In further control experiments, in which water was injected into the intestine instead of a dextrose solution, the inhibited rate of absorption was also marked, so that clearly it is not possible to state that carbohydrate in the intestine had in itself an inhibitory effect.

The effect of a dextrose solution is seen in Experiment 130. In cat *B* 25 c.c. of a 10 per cent. solution of dextrose were injected into the small intestine 15 minutes before the β-i solution was injected. Cat *A* was the control, and only received the β-i solution. 70 per cent. of the β-i was absorbed from the intestine of *A* in 1½ hours, while 49 per cent. was absorbed from the dextrose cat. Here, then, is a marked inhibitory effect apparent in the dextrose cat.

(*e*) *The effect of water.*

That the foregoing effect may be due to the water of the solution and not the dextrose is apparent from Experiments 57 and 58.

In Experiment 57, 60 c.c. of Ringer solution were injected into the intestine at the duodeno-jejunal flexure of cat *A*, 40 minutes before the β-i was injected. No fluid was injected into *B* except the β-i solution. *A* only absorbed 33 per cent. of the injected β-i in 1 hour 40 minutes, compared to the 70 per cent. absorbed in *B*.

In Experiment 58, where 25 c.c. of Ringer solution were injected into *A*, a similar, but not so pronounced a result, was obtained.

Inference: The inhibitory action on the absorption of β-i from the intestine, evident when a carbohydrate solution has been previously placed in the intestine, cannot be ascribed to the carbohydrate itself, because Ringer solution has a similar marked inhibitory action.

(f) The effect of bile on the absorption of β-i.

While discussing the effect of food-stuffs in the intestine on the absorption of β-i, it is right that the effect of bile should be considered at the same time. For it is evident that one of the effects of food passing from the stomach into the duodenum is a liberation of bile. It is necessary therefore to see whether the increased flow of bile may account for some of the effects previously demonstrated.

From another point of view, the inquiry into the effect of bile is interesting. In diarrhoea and vomiting of children, one of the results must be the ultimate deficiency of bile salts and other bile products in the child's economy, following from the persistent intestinal condition. It is further evident that the body values its bile salts, for otherwise the cycle of events which it employs, namely, the excretion by the liver and subsequent reabsorption into the portal circulation, would not occur with such persistence and regularity. The elimination of bile may therefore be of some importance in the aetiology of diarrhoea and vomiting.

In addition to these facts, the important part played by bile in allowing purgatives like aloes and rhubarb to have their full physiological effect seems to indicate that it may have some action on the absorption of substances from the intestine.

In the experiments performed in this connexion it will be seen that bile has some inhibitory action on the absorption of β-i from the intestine, and there is also evidence that this action depends on the bile salts present.

In Experiment 105, 1 c.c. of the cat's own bile withdrawn from the gall bladder was placed in each of two loops of the intestine, while in an intermediate loop no bile was injected. In $2\frac{1}{2}$ hours 66 per cent. of the injected β-i was absorbed from the control loop, while 50 per cent. and 34 per cent. were absorbed from the bile-containing loops.

In Experiment 106, where $\frac{1}{2}$ c.c. of bile was injected into one loop, 60 per cent. of β-i was absorbed from this loop containing bile in the time that 90 per cent. disappeared from the control loop.

We see, therefore, that bile depresses the rate of absorption of a toxic substance like β-i. It may be added that the results obtained with bile at the duodeno-jejunal end of the small intestine were not consistent, and the effect in any case was not so clear as at the caecal end.

Experiments 108 *a* and 108 *b* further indicate that bile salts alone are capable of inhibiting the action of β-i. In these experiments it will be seen that less β-i has been absorbed from those loops which contain bile salts than from those without bile salts. One must be careful in the use of bile salts, for they

have such an irritant action on the intestinal mucous membrane that it is easy to cause an inflammatory condition in the intestine by means of them, and this inflammation itself will naturally depress absorption. An effort was therefore made to keep the amount of bile salt in the intestine at an amount likely to be met with normally, and below the amount capable of producing an inflammatory condition of the epithelium. In the bile-salt experiments a solution containing 6 per cent. sodium glycocholate and 2 per cent. sodium taurocholate was used, and 0·25 c.c. was injected into the loop of intestine with the 5 c.c. of 1 per cent. β-i.

The results here described seem to me to be important from a practical point of view, and it may well be that the deficiency of bile salts will prove to be one of the factors worthy of further consideration in the case of diarrhoea and vomiting of children.

Whether bile salts play any such part as this in normal life seems to depend, in view of the above results, on whether they are absorbed back into the blood-stream in the upper or lower part of the small intestine. If they are normally absorbed for the most part from the jejunum, then it would not appear that they will have much opportunity of exerting any inhibitory influence on the absorption of toxins formed in the ileum. Two further points are suggested by these results :

1. It has been seen that all the feeding-experiment results indicate that food in the intestine inhibits the normal absorption of β-i. The result of feeding is always to increase the amount of bile in the intestine, and the depressed absorption of the β-i may therefore be due to the bile present.

2. The presence of bile in the intestine, even in localized patches, as is evident by the pigmentation, is a condition which may be met with in any intestinal experiment. Consequently, one has always to be careful in observing this factor in absorption experiments.

Summary. In this section it has been demonstrated that the presence of food-stuffs and water in the intestine delays the absorption of β-i contained in a watery solution. An inhibitory effect is also produced when bile or bile salts are present. In other words, an empty non-digesting intestine is in the best condition for absorbing into the general circulation a toxic substance like β-i.

V. *The Effect of* $MgSO_4$ *on the Absorption of* β-i.

The effect of magnesium sulphate on the absorption of β-i from the intestine can be tested either by giving the salt by mouth and then injecting the β-i into loops of the intestine, or by first injecting magnesium sulphate and then β-i into the same loop. The former of these methods is the better, because it conforms more exactly to the normal; but it is very difficult to perform, for, when $MgSO_4$ is given to a cat with an empty stomach, it is immediately vomited. The results to be described were therefore obtained by the second method.

In Experiment 137 it will be seen that 30 per cent. of the β-i injected was

absorbed from the loop containing $MgSO_4$, and 56 per cent. from the control loop containing no $MgSO_4$.

In Experiment 138, 33 per cent. of the β-i in the $MgSO_4$ loop was absorbed, while from the control loops containing no $MgSO_4$ 76, 66, and 69 per cent. of the β-i disappeared. In these two experiments the amount of $MgSO_4$ present was 6 per cent., and undoubtedly with a higher concentration of the salt the depression of the absorption would be greater. On weakening the $MgSO_4$, however, a limit is reached below which this salt has no effect. This can be seen in Experiment 136, where the amount of $MgSO_4$ in the loop was 0·83 per cent., and there is no inhibition in the rate of absorption.

The effect of $MgSO_4$ is no doubt complicated by other factors which I have not up to the present been able to test. Just as its cathartic properties depend upon the amount of fluid in the body, so also it cannot be doubted that the effect of $MgSO_4$ will be considerably greater in a normal individual than in one already deprived of fluid, as is met with in the case of diarrhoea and vomiting. What strength of $MgSO_4$ in an animal with deficient body-fluids is necessary to inhibit the absorption of toxic substances from the intestine can only be ascertained by further work.

Summary. Experiments have been performed to show that a strong solution of $MgSO_4$ (6 per cent.) has a depressant action on the absorption of β-i from the intestine, whereas a weak solution (0·8 per cent.) has no such effect. Experiments with strengths varying between these limits show that a solution as low as 2 per cent. in the normal animal exhibits this depressant effect.

VI. *The Effect of Morphine on the Absorption of β-i.*

Morphine is so often used in cases of intestinal disturbance, and with such beneficial results, that its effect on the absorption of β-i from the intestine was investigated. In these experiments two difficulties arose, each of which made the results more complicated:

1. The direct depressant action of the morphine on the respiratory centre, even in small doses.

2. With this depressed respiratory centre, the animals are on the point of death for some time before actual death occurs, and it is doubtful whether any absorption takes place during this period.

In spite of these difficulties, however, experimental results show that although morphine may have some depressing influence on the absorption of toxins from the intestine, yet the effect is small and more than counterbalanced by more serious results.

In Experiment 134 there is seen the effect of 5 minims of the liquor morphinae hydrochloridi placed in two loops of the intestine. In these morphine-containing loops, 50 and 55 per cent. of the β-i injected were absorbed in the time that 55 and 66 per cent. of β-i were absorbed from the corre-

sponding control loop containing no morphine.   The inhibition of the morphine on the absorption is small.

In order to see whether one could completely suppress the absorption of β-i by morphine, Experiment 133 *b* was performed, in which a larger dose, i.e. 1 c.c. of the liquor morphinae hydrochloridi, was injected into the intestine along with the β-i.   In this experiment, after a period of 70 minutes, 37·5 per cent. and 40 per cent. of the β-i had been absorbed.   It is clear, therefore, that morphine, even in large doses, allows considerable absorption of a toxic substance like β-i from the intestine.

A more serious point of consideration is, however, that in all the experiments performed, the morphinized cats died of respiratory failure.   The importance of this will be discussed at the end of the paper.

Summary.   Morphine seems to depress slightly the absorption of β-i from the intestine, but this inhibitory action is negligible in view of the dangers of respiratory failure caused by the morphia in these experiments, even when used in comparatively small doses.   These experiments suggest that there is considerable danger in the use of morphia in cases of diarrhoea and vomiting in infants.

VII.   *The Effect of Alkali and Acid on the Absorption of β-i.*

Differences of hydrogen ion concentration met with in the digestive tract play such an important part in ferment action and other functions of the alimentary canal that it was thought probable that they would also play an important part in absorption and, from the point of view of this research, in the absorption of β-i.   Experiments were therefore made to test this point.

Alkali.

Two points of interest are noticeable about these experimental results :

1. Alkali has a greater adjurant action in the absorption at the upper than at the lower end of the small intestine.

2. That the amount of increased absorption due to the presence of alkali varies very considerably at different parts of the intestine and even in the same part of the intestine in different cats.

As for the first point, a possible reason why alkali is more potent at the jejunal end than at the ileal end is that the normal reaction of the mucous membrane at the latter end is more alkaline, and this may be the optimum condition of alkalinity for absorption in this position.   It may in itself also explain why absorption from the lower end of the small intestine is normally greater than from the upper end.   As regards the second point, the marked difference in the effect of the added alkali is not surprising when one considers the variations in reaction met with in the intestine even in corresponding parts.

In Experiment 120 is seen the effect of alkali at the jejunal end of the small intestine.   To one loop was added 1 c.c. of 5 per cent. Na_2CO_3, and from this

loop 82 per cent. of the β-i was absorbed in 2 hours 34 minutes, while 50 per cent. only disappeared in the same time from the control loop containing no alkali.

In the ileum (Experiment 133 a) the same amount of alkali, viz. 1 c.c. of 5 per cent. Na_2CO_3, was injected into one loop, and from this loop 69 per cent. of the β-i was absorbed, compared with 62·5 per cent. from the control loop.

It will be seen there is a marked increase in the β-i absorbed under the influence of alkali at the jejunal end, whereas at the ileum the increase is small.

Acid.

One definite remark which can be made about the presence of acid in the small intestine is that, if it is allowed to remain free in the intestine, then there is a marked inflammatory condition set up, the blood-vessels are congested, and the mucous membrane reacts as if to a great irritant, a large amount of mucus being secreted and the mucous membrane denuded. The underlying muscle also becomes congested. It is true that small quantities of acid can be placed in the intestine without irritating the mucous membrane, but this, I think, is due to the presence of neutralizing substances, such as alkali and protein, already present or immediately secreted when the acid is injected. For instance, it is possible to inject stronger acid solutions into the lower end of the small intestine than into the jejunal end without producing the irritant action. This is to be correlated with the larger amount of neutralizing alkali at the lower end.

My results point to the probability that acid stops the absorption of β-i absolutely when it destroys the mucous membrane, and inhibits it only below this point. Lactic acid, 0·6 per cent., delays the absorption of β-i, and an increase of acid above this figure prevents absorption and destroys the mucous membrane. I have obtained no evidence that the addition of acid in any quantity can stimulate the absorption of β-i. It is interesting to see how differently the intestine reacts to acid and alkali, how susceptible it is to the former, an inflammatory condition being easily set up, and how indifferent it is to the latter, even to much larger quantities. The effect of these substances on the absorption of β-i is in keeping with the different results on the mucous membrane which are noticed when acid and alkali are brought into contact with them.

Summary. Alkali stimulates the absorption of β-i from the small intestine, and more especially at the jejunal end, the effect at the ileal end not being so obvious.

Acid has an inhibitory action on the absorption of β-i, and a small concentration completely stops absorption and destroys the epithelium of the mucous membrane.

VIII. *The Effect of altering the Volume of Body Fluids on the Absorption*
of β-i.

It is well known that an animal has an excellent mechanism for keeping its blood-volume constant, in spite of conditions tending to produce alterations. Thus, bleeding an animal causes fluid to be withdrawn from the lymph and other fluid dépôts, whereas injecting saline into the circulation causes the excess of fluid to accumulate in the splanchnic and other veins, and subsequently to be passed on to the lymphatic spaces before being finally excreted by the kidneys.   It is, therefore, difficult to raise the arterial blood-pressure by the injection of fluid, although, if the arterial blood-pressure is low to begin with, in consequence of a deficiency of body fluid, then the injection of water does have a more pronounced heightening effect on it.   It will be seen therefore that the injection of Ringer solution into the blood-stream does not make as important a difference to the arterial and capillary circulation as might at first be expected.   Previous experiments described have been concerned only with the effects of the intestinal contents on the absorption of β-i, but it is evident that the blood circulating through the intestine is also of great importance.   As to what is the relative importance of the various factors in the blood, such for instance as the blood-pressure, blood-volume, viscosity, and osmotic pressure in regulating absorption from the intestine, very little is known.   No great effort has been made in this research to differentiate between these factors, but the experiments described below demonstrate clearly that absorption from the intestine can be readily modified by varying the blood circulation.

(a) *The effect of diminishing the body fluids by bleeding.*

When this type of experiment was first attempted, it was with the idea that the condition might be comparable to that of an animal deficient in body fluids, such as is met with in diarrhoea and vomiting of children or when an animal has had fluid withheld from its diet.   It is obvious, however, that the conditions set up by withdrawing blood cannot be regarded as equivalent to that resulting from an abnormal loss of fluid through the kidney or alimentary canal, or produced by withholding water from the diet.   The bled animal has a deficient cellular and protein element in its blood, and its blood-volume may be quickly restored to the normal by the mechanism mentioned above.   Though the experiments are not comparable to the condition aimed at being produced, the results seem to be sufficiently interesting to merit description.

In Experiment 140, 40 c.c. of blood were withdrawn from the carotid artery in one cat.   In this cat 50 and 66 per cent. of the β-i injected into the intestine were absorbed, whereas in the control normal cat 75 and 80 per cent. were absorbed from corresponding loops of the intestine during the same time.

In Experiment 141, 15 c.c. of blood were withdrawn from the carotid artery three minutes before the β-i was injected into the intestine, and in thirty minutes 20 and 33 per cent. of the β-i were absorbed, comparing with 33 and 39 per cent. absorbed from the intestine of the control cat.

It is evident from these two experiments that the effect of bleeding is to diminish markedly the absorption of the β-i from the intestine.

To set against this inhibited absorption of a toxic substance, there must however be placed the fact that the bled cat has lost a great amount of its power to resist the toxic substance which is absorbed. For instance, in Experiment 140, the fall of blood-pressure caused by the absorbed β-i in the fed cat was 40 mm. Hg, whereas in the bled cat, although less β-i was absorbed, the fall in blood-pressure was 68 mm. Hg. In Experiment 141 the bled cat died thirty minutes after the injection of the β-i into the intestine.

Experiment 56 shows very well this greatly diminished resistance resulting from bleeding. 30 c.c. and 20 c.c. of blood were withdrawn respectively from cats B and C before injecting β-i into the intestine. Cat B died fifteen minutes, and cat C ten minutes, after the injection of β-i. Cat A, the control cat with no blood withdrawn, lived $3\frac{1}{4}$ hours after the injection, during all of which time the β-i was being absorbed into the blood-stream.

It is evident from the above-described experiments that bleeding has two effects:

1. It diminishes the rate of absorption of β-i from the intestine.

2. It reduces very greatly the resistance of the animal to the toxic substance absorbed.

I have no doubt in my own mind, from other experiments described in this paper, that an animal deficient in body fluids caused by loss through the alimentary canal or kidney would absorb β-i at a greater rate than the normal animal, and in this respect be different from the bled animal.

Summary. A bled animal absorbs a toxic substance from the alimentary canal at a less rate than a normal animal, but it has but little power of rendering such an absorbed substance innocuous, and rapidly succumbs.

(b) *The effect of increasing the body fluids by injecting Ringer solution.*

It can be definitely stated that any large increase of the body fluids caused by injecting Ringer solution into the blood-stream has a definite inhibitory action on the absorption of β-i from the intestine. That is, in the case of cats, the injection of quantities of fluid greater than 100 c.c. has this inhibitory effect. Quantities of fluid below this amount do not appear, from the experimental results obtained, to have such an action. However, it must be remembered that the problem is somewhat complicated, and this may explain the indefinite results obtained when smaller quantities of solution than 100 c.c. were injected into the blood-stream. This complication is as follows: If an animal has but small power of resistance to β-i, as is the usual condition of a control non-digesting animal, the first β-i absorbed from the intestine brings the blood-pressure down very rapidly from 110–120 mm. Hg to 50–60 mm. Hg, the respiratory centre is affected, and the animal may be on the point of death for some time. During this time the further absorption of β-i seems to stop, or is depressed, while the Ringer injected cat, being in a better position for

metabolizing the absorbed β-i, continues to absorb it, and may ultimately, over a definite period of time, absorb as much as the control cat.

When large quantities of Ringer solution are injected, two definite results are obtained : (1) the animal's power of absorbing β-i from the intestine is markedly depressed, (2) the animal has a greatly increased power of resistance to the β-i absorbed.

Before describing the results of experiments performed, it may be well to mention one other important fact. It is useless in such experiments, where the animal has to be left on the operating table for periods over one hour, and where a salt solution is injected into the blood-stream, to use ether, chloroform, or A.C.E. as anaesthetics in cases. When fluid is injected into animals anaesthetized in this way, oedema of the lungs is frequently produced, and this may kill the animal and certainly deprives the results obtained of any real value. In such experiments, therefore, I found it necessary to use urethane to such an amount that little or no other anaesthetic was necessary. Urethane, however, has its disadvantages : (1) urethane itself depresses the respiratory centre ; (2) although the initial blood-pressure under urethane is high, yet it seems to make the vasomotor system more susceptible to depressant substances such as β-i.

(b) 1. *The injection of large quantities of Ringer solution into the blood-stream.*

Experiments 50 and 52 show the effect of injecting several hundred c.c. of Ringer solution. In Experiment 50 quantities of 200, 100, and 100 c.c. were injected into the external jugular of one cat. During the time of absorption, viz. 1 hour 50 minutes, 25 and 35 per cent. of the β-i were absorbed from the intestine, the control cat, without fluid injection, absorbing 40 and 70 per cent. in the same period. When the time allowed for absorption is increased, as in Experiment 52, the time in this case being 2 hours 40 minutes, the difference is less marked, especially if, as usually happens, the control cat dies. In this experiment, quantities of 200, 100, and 100 c.c. were injected, and the amounts of β-i absorbed were 50 and 82 per cent. in the Ringer cat and 66 and 89 per cent. in the control cat.

(b) 2. *The frequent injection of small quantities of Ringer solution into the blood-stream.*

It seemed probable that, in view of the mechanism animals possess for ridding the circulatory system of excessive fluid, the injection of small quantities of fluid at frequent intervals would be more efficacious in suppressing the absorption of β-i than the injection of large volumes of fluid less frequently. For, in the former case, the circulatory system would probably, over the period of the experiment, have an average greater quantity of fluid circulating through it. Experiment 110 was carried out to test this point. Into the external jugular vein of one cat, quantities of 10 c.c. of Ringer solution were injected at intervals of fifteen minutes, 110 c.c. being injected altogether. 50 and 73 per cent. of

the β-i in the intestine were absorbed by the Ringer cat, and from corresponding intestinal loops of the control cat without Ringer solution 80 and 84 per cent. of the β-i disappeared.

In all the other seven experiments in which large quantities of Ringer, solution were injected, there was marked depression of the β-i absorbed from the intestine.

Of greater importance still, is the fact that in all the experiments of this nature performed, viz. ten, eight of the control cats, i.e. those without the injection of fluid, died. In one case only did the Ringer-injected cat die, and this took place after thirty minutes' further β-i absorption than the control cat. In several cases the Ringer cats were allowed to live for some hours after the control cats had died, and had ultimately to be killed.

The result of these experiments is, therefore, quite definite.

1. The absorption of a toxic substance like β-i is depressed by the injection of large quantities of Ringer solution.

2. The resisting power of a Ringer-injected cat is greatly increased against the toxic action of β-i.

(b) 3. *The injection of small quantities of Ringer solution into the blood-stream.*

Other experiments similar to those already described were performed, but in these cases smaller quantities of Ringer solution were injected (75 c.c. or less over the whole period of the experiment). None of these will be quoted, as the difference between the β-i absorbed in the experimental and control cats was too small to be of any importance.

IX. *Some Miscellaneous Experiments.*

In the following experiments only one of each type of experiment was performed, and it is impossible therefore to attach importance to them as they stand. The only one that points to any positive result is the first, where the osmotic pressure of the blood was increased by injecting dextrose into the blood-stream.

The effect of increasing the osmotic pressure of the blood by injecting dextrose solution. Dextrose was used in this experiment for two reasons :

1. It is a suitable means of raising the osmotic pressure of the blood by a non-toxic physiological substance.

2. It is commonly believed that carbohydrate plays an important part in neutralizing toxic substances, so that the injection of dextrose was hoped to increase materially the resistance of the animal to β-i.

In Experiment 143 it will be seen that 25 c.c. of 100 per cent. solution of dextrose were injected into the external jugular vein immediately before the β-i solution was injected into the intestine. After one hour of absorption, 55 and 64 per cent. of the β-i had left the intestine of the dextrose cat, and 37 and

55 per cent. in the case of the control cat. The dextrose cat died one hour from the time of injection.

This experiment seems to indicate :

1. That increasing the osmotic pressure of the blood increased the rate of absorption from the intestine.

2. That the animal's resistance was not increased by the dextrose, since this cat died.

The effect of injecting magnesium sulphate into the circulation on the absorption of β-i from the intestine. $MgSO_4$ injected into the circulation is said to have some of the distinctive actions that are associated with this substance in the intestine. For instance, when injected subcutaneously, $MgSO_4$ increases intestinal peristalsis and may produce purgation, and it is therefore believed that some of the $MgSO_4$ injected subcutaneously is passed back from the blood into the gut. From this fact it might be expected that the injection of this substance into the blood would affect the rate of absorption from the intestine. Against such an expectation, however, may be placed the fact previously demonstrated that it takes a concentration of 2 per cent. $MgSO_4$ in the intestine to have any marked depressant action on the absorption of β-i.

In Experiment 115 two lots of 25 c.c. of Ringer solution containing 0·5 per cent. $MgSO_4$ were injected into the external jugular vein. After 65 minutes of absorption, 53 and 73 per cent. of the β-i had disappeared from the intestine of the $MgSO_4$ cat, and 53 and 50 per cent. from the corresponding loops of intestine of the control cat.

This experiment indicates that :

$MgSO_4$ in the circulation has not diminished the rate of absorption of β-i from the intestine.

The effect of injecting secretin into the blood-stream on the absorption of β-i from the intestine. On the supposition that absorption from the intestine is a kind of inverted secretion, it is possible that, just as the pancreas is stimulated to activity by secretin, so also this substance might have some action on absorption from the intestine. To test this point, Experiment 47 was performed.

Secretin was made in the ordinary way from the mucous membrane of the duodenum of a cat, and injected at different periods into the external jugular vein of another cat absorbing β-i from the intestine. The total amount of secretin injected in 3 hours was 100 c.c. The control cat died after 2¼ hours. The amounts of β-i absorbed from the secretin cat were 80 and 80 per cent., and from corresponding loops in the control cat 83 and 75 per cent.

The following points are indicated by this result :

1. Secretin has had no stimulating effect on the absorption of β-i (this cat absorbed for ¾ hour longer than the control).

2. The increased vitality of the secretin cat can probably be associated with the injection of fluid into its blood-stream.

X. *Evidence that β-i is not absorbed from the Large Intestine.*

In any consideration of the subject of alimentary toxaemias, it is clearly necessary that absorption of toxic substances from the large intestine must be investigated, for this situation is generally regarded as the abode of undesirable and toxic substances, and, if absorbed, they would probably produce pathological symptoms. The subject is, however, a large and complicated one, and the facts so far ascertained in this research can but form the basis of further work, although they were thought sufficiently interesting to mention in this paper.

In considering the part played by β-i in the large intestine, the following questions present themselves for solution :

1. Is β-i normally formed in the large intestine ?

2. If formed, is it absorbed into the blood-stream ?

3. If formed and not absorbed, does it have a local action on the colon or is it further changed to an innocuous substance ?

As regards Question 1, there is no doubt but that β-i can be formed in the intestine, for, in this position, Twort and I constantly found the bacillus which produced β-i from histidin. On the other hand, so far as I am aware, nobody has isolated β-i from the contents of the colon or even from its mucous membrane. I should think it unlikely that β-i is formed to any real extent in the large intestine of a normal animal, for its presence would stimulate the plain muscle, and bring about evacuation when only a small quantity was present.

As regards Question 2, this point has been investigated, and it will be seen that no evidence of the absorption of β-i from the large intestine has been obtained. It does not seem to me likely that such a substance would be absorbed in this part of the alimentary canal, for the following reasons : (*a*) There is but little evidence that anything except water is absorbed from the large intestine ; (*b*) It is obviously undesirable that toxic substances which accumulate in the large intestine should gain access to the blood and general circulation.

As regards Question 3, it will be seen that if β-i is formed in, or enters the large intestine from the small intestine, then bacteria can, and probably do, convert it into an innocuous substance.

In Experiment 71 we see that all the β-i injected into the large intestine was recovered after it had been allowed to remain there 1 hour 55 minutes. From a loop of small intestine placed immediately above the ileo-caecal valve, 40 per cent. of β-i was absorbed in this time. This experiment seemed to indicate that the large intestine was incapable of absorbing β-i. When the experiment was subsequently repeated, however, a different result was often obtained, namely, some of the β-i injected into the large intestine could not be recovered.

Experiment 132 is an example of this result. It will be seen that 50 and 50 per cent. of the β-i disappeared from loops of the small intestine, and 30 per cent. from the large intestine. In view of the contradiction of these experimental results, Experiment 144 *c* was performed, in which, before

injecting β-i into the large intestine, all the blood-vessels to this part were tied. In 2 hours 20 minutes, 33 per cent. of this β-i disappeared, and since it could not be absorbed it had obviously been destroyed by bacterial decomposition and the end products, at least so far as its action on plain muscle was concerned, were without physiological action.

The above facts indicate that the following statements concerning β-i and its relation to the large intestine may be true :

1. That any β-i formed in the large intestine or passed on here from the small intestine is not absorbed into the general circulation.

2. That, as a rule, any β-i formed in the large intestine is further destroyed by bacteria and made harmless, so that it does not even have its local stimulating action on this organ.

The complexity of the subject is emphasized by the different actions bacteria have on histidin as determined by the presence or absence of extraneous factors like oxygen, sugars, acids, and alkalis, and no doubt other unknown influences. It is an interesting problem to consider what part is played by β-i in the production of diarrhoea, and if it is responsible, why in such cases it has not been destroyed by other bacteria. For it is clear that β-i is not absorbed from the large intestine, and if formed, will only bring about evacuation of the colon and rectum.

As to what end product is formed when the bacterial flora of the large intestine makes β-i inactive, but little can be said. This is a change easily carried out, and only requires the removal of ammonia from the β-i molecule. That a considerable amount of ammonia is removed by bacteria in the colon is evident from the work of Folin, who goes so far as to claim that all the ammonia found in excess in the portal circulation really comes from the large intestine as the result of bacterial decomposition. This power possessed by bacteria in the large intestine of rendering toxic amines innocuous seems to me a factor of some importance, and worthy of further consideration, for it is almost certain that all active amines would undergo the same fate as that which obtains in the case of β-i.

Mutch (8) has recently found that the presence of the Bacillus aminophilus in the ileum is characteristic of patients suffering from chronic constipation, and associated with this, a low blood-pressure and toxaemic condition. It may be mentioned that the Bacillus aminophilus removes carbon dioxide from histidin and forms β-i, and Mutch assumes that the formation and absorption of β-i from the ileum is responsible for the low blood-pressure.

My results, here described, are in agreement with those of Mutch, in so far as it is the small intestine and not the large intestine which is the position for the absorption of β-i, if it should happen that this substance is responsible for the toxaemic symptoms of chronic constipation. It seems to me there are too many difficulties still unexplained by the meagre facts so far ascertained, to allow the claim that the production and absorption of β-i in the ileum cause a toxaemic condition in such people. To mention one obvious difficulty, an increased

formation of β-i would mean a hurried evacuation of the contents of the intestine rather than a condition of constipation, and I doubt whether any physical disability of the ileum and colon, short of complete obstruction, would satisfactorily meet this difficulty. In fact, it seems impossible with our present knowledge of bacterial production, bacterial destruction, and the absorption of β-i in the intestine, to be able to claim any causal relationship between chronic alimentary toxaemias and this substance.

Summary.

1. No evidence of the absorption of β-i from the large intestine was obtained.

2. Where β-i has disappeared after injection into the large intestine, it can be satisfactorily explained by bacterial decomposition.

3. This change of a toxic physiological substance into an inactive substance in the large intestine may extend to all amines. If this is so, it is an important second line of defence against the entry of such substances into the blood-stream from the large intestine.

XI. *The Resistance of Animals to β-i under Varying Conditions.*

In order to gain some insight into the processes underlying the resistance offered to β-i by animals under varying conditions the blood-pressure effects were specially studied.

The blood-pressure of the animals in these experiments depends on two factors :

1. The rate of absorption of β-i into the blood. The greater the amount absorbed, the greater the fall of blood-pressure.

2. The rate at which the animal can metabolize the absorbed β-i. If the β-i can be rendered innocuous immediately on absorption, naturally there is no effect on the blood-pressure.

The action of β-i on the blood-pressure is complex, and is not understood by physiologists. The outstanding points about its action are :

1. That it is an extremely strong stimulant of all plain muscle, and outside the body constricts all arteries.

2. That in the intact animal it lowers the general blood-pressure and dilates the arterioles of the systemic system.

The difference between these two actions can only be reconciled by assuming that β-i either has a paralysing effect on the vasomotor centre or on some part of the sympathetic nervous system. That it does affect the central nervous system is evident from the anaesthetic action of the drug; for it is nearly always possible to predict the relative amount of β-i absorbed during an experiment by the amount of anaesthetic required to keep the animal anaesthetized. An animal absorbing β-i rapidly does not require so much anaesthetic as one absorbing it slowly. It is further clear that β-i has a depressant effect on the respiratory centre, for whenever a cat has died under its influence, it has been observed that it is the respiratory centre that fails. It is true that the effect of injecting β-i

into the blood-stream is to cause a more rapid and a deeper respiration, but this effect is due to the constriction of the bronchiole muscles, which makes the breathing efforts more difficult because of the resistance met by the ingoing and outgoing respiratory air.

The next preliminary question is—what does the body do with β-i when it metabolizes it and renders it innocuous?   Here again we are on unknown ground, but arguing by the analogy of other animes (9) one can say that its mode of disposal is probably as follows: The β-i is, probably, after absorption into the portal circulation, attacked by the liver cells, and the amino group taken away thus:

It seems probable, therefore, that the fall in general blood-pressure is due to the depressant action of β-i on the vasomotor centre or sympathetic system, which more than counterbalances its direct contracting action on the plain muscle of the arteries.

$$\begin{array}{cc} NH-CH \\ | \hspace{2em} \diagdown \\ CH = N \hspace{0.2em} \beta\text{-i} \end{array} C \cdot CH_2CH_2NH_2 + H_2O = \begin{array}{cc} NH-CH \\ | \hspace{2em} \diagdown \\ CH = N \end{array} C \cdot CH_2CH_2OH + NH_3$$
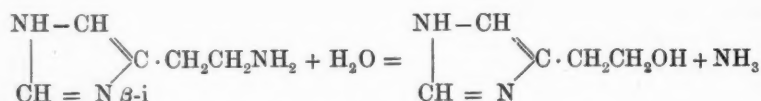
The alcohol group is probably then oxidized to—

$$\begin{array}{cc} NH-CH \\ | \hspace{2em} \diagdown \\ CH = N \end{array} C \cdot CH_2COOH$$

β-imidazolylacetic acid.
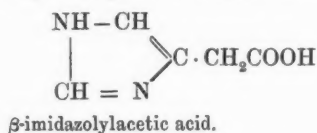
Some of this acetic acid compound may then be combined with glycin and excreted as the aceturic compound thus:

$$\begin{array}{cc} NH-CH \\ | \hspace{2em} \diagdown \\ CH = N \end{array} C \cdot CH_2 \cdot CO \cdot NHCH_2COOH$$
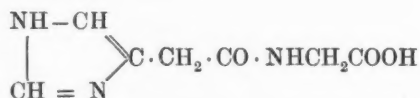
These chemical changes are those undergone by parahydroxyphenylethylamine and indolethylamine, the bases of the amino-acids tyrosin and tryptophane respectively (10).   So far as I know, the above chemical changes have not been shown to occur to β-i, at least in the perfused liver.   One would expect there would be difficulty in proving the reaction with a substance of such marked physiological potency.   I wish to point out that all that is necessary to render β-imidazolylethylamine innocuous is to remove the NH_2 group.

It was hoped, during the course of these experiments, to find there would be some simple relation between the rate of absorption of β-i and the blood-pressure. If, for instance, in animals placed under similar conditions, one animal could metabolize the β-i as it was absorbed, and so retain a high blood-pressure, while the second animal, with a poor metabolizing power, had a low blood-pressure, it might be expected that the rate of absorption would be a measure of the blood-pressure, so that an animal with a vigorous metabolism would absorb more β-i

than one with a poor metabolism. This condition cannot be said to hold from the experiments so far performed, although, I believe, when the blood-pressure is very low—say below 50 mm. Hg—the absorption from the intestine is small.

Normal Blood-pressure Changes during the Absorption of β-i.

In all experiments the blood-pressure is at its lowest about thirty minutes after the β-i has been injected. If the animal has but little resisting power to the absorbed β-i, then the blood-pressure remains stationary for some time, until a further fall of pressure occurs with death. If the animal has a more vigorous metabolism, a reaction follows and the blood-pressure gradually rises, sometimes even to the normal, but more frequently to a level lower than the normal.

The usual blood-pressure effects are to be seen in the following experiments:

Experiment 140 *a*.					*Experiment* 140 *b*.				
β-i injected into intestine, 12.25.					β-i injected into intestine, 12.33.				
Blood-pressure.					*Blood-pressure.*				
Before injection, 12.18			120 mm. Hg.		Before injection, 12.30			96 mm. Hg.	
After	,,	12.29	103	,,	After	,,	12.36	79	,,
,,	,,	12.35	86	,,	,,	,,	12.43	65	,,
,,	,,	12.45	80	,,	,,	,,	12.51	55	,,
,,	,,	12.50	62	,,	,,	,,	1.2	58	,,
,,	,,	12.55	52	,,	,,	,,	1.16	60	,,
,,	,,	1.3	56	,,	,,	,,	1.30	60	,,
,,	,,	1.17	60	,,	,,	,,	1.55	70	,,
,,	,,	1.38	60	,,	,,	,,	2.10	74	,,
,,	,,	1.55	78	,,					
,,	,,	2.14	76	,,					

This lowering of the blood-pressure and subsequent rise may be correlated with the rate of absorption of β-i, which is greater during the first hour, and afterwards becomes slower.

(a) *The blood-pressure effects in animals injected with Ringer solution.* It has previously been pointed out that injecting large quantities of Ringer solution into the blood-stream has two effects:

1. It delays the absorption of a toxic substance like β-i from the intestine.

2. It makes the cat less susceptible to the β-i absorbed, so that, whereas the control cat usually dies, the Ringer-injected cat lives.

The question is, how does the Ringer solution have this second action?

This question is difficult to answer, but it seems quite definite that the increased fluid does not prevent the β-i from lowering the blood-pressure, almost in as marked a manner as in the control animal. It does, however, prevent the final lowering of blood-pressure preceding death.

That the injection of fluid does not prevent the initial lowering of blood-pressure is seen in Experiment 110. In this experiment it will be seen that the blood-pressure is depressed from 110 mm. to 60 mm. in the Ringer-injected cat and from 120 mm. to 70 mm. in the control cat. It will be further observed that the blood-pressure of the Ringer cat gradually rises to 86 mm., while that of the control cat gradually sinks to 64 mm., at which time the fall is rapid and the cat

dies in five minutes.   In other words, the injection of fluid does not prevent the initial large fall in blood-pressure, but gives to the animal the power of asserting itself once more, and the blood-pressure rises to some extent.

The question now arises, why does the Ringer solution prevent the fall of blood-pressure preceding death?   I have already mentioned that I do not consider the fall of blood-pressure to be the primary cause of death.   Death in these animals undoubtedly is the result of the failure of the respiratory centre. Of course the activity of the respiratory centre depends on the blood-pressure, but a Ringer-injected cat will have an efficient respiratory centre with a lower blood-pressure than a non-injected control cat will have with a higher blood-pressure.   One must further suppose that the β-i depresses the vasomotor centre as well as the respiratory centre, for the asphyxial rise of blood-pressure, due to the increased hydrogen in concentration of the blood which accompanies respiratory failure, is absent.

The beneficial effect of injecting fluid into these cats depends, therefore, on some effects produced in the medulla oblongata which prevent the β-i from completely knocking out of action the respiratory and vasomotor centres.   From this consideration, it appears possible that the original fall of blood-pressure, experienced to an equal extent both by the Ringer-injected and the control cats, may depend upon some interference of the vasomotor mechanism not situated in the medulla oblongata, and for this reason, that whereas injected fluid does not prevent the normal fall of blood-pressure produced by β-i, it does prevent the onset of that fall of pressure and failure of the respiratory mechanism accompanying death, the latter of which actions are obviously related to the medulla oblongata.

Two suggestions can be made as to the increased resistance conferred on animals by injecting Ringer solution :

1. A large part of the Ringer solution injected must be filtered off from the blood to the lymph spaces.   This in itself may carry off a portion of the β-i to places where it is innocuous.

2. The increased body-fluids may increase the gaseous and other interchange between the blood, the lymph, and the cells of the body, including the cells of the nervous system.   The cells would consequently get a greater opportunity of selecting nutriment, and therefore be in a position for resisting more completely the full toxic action of the β-i.

There does not appear to me to be any definite evidence to allow one to state that β-i can be rendered innocuous at a greater rate when the body fluids are increased by injecting saline solutions into the blood.   On the other hand, the beneficial results of such treatment, as seen by the increased vitality of the animals, are unmistakable.

Summary.   Injecting fluid into the blood-stream does not prevent the fall of blood-pressure caused by β-i as seen in the normal animal; but it does prevent the fall of blood-pressure preceding death.   This latter important action probably depends on the increased vitality of the centres in the medulla.

(b) *Blood-pressure effects in animals deprived of blood.* Loss of blood makes an animal very susceptible to β-i absorbed from the intestine, and although less is absorbed than in the normal animal, as has been previously shown, the bled animal always dies as the result of the experiment, and often very rapidly. The animal seems to lose most of its power of rendering the β-i innocuous, the blood-pressure rapidly falls and the respiratory centre fails.

In Experiment 141, after withdrawing 15 c.c. of blood from the carotid artery, β-i absorbed from the intestine brought the blood-pressure down from 90 mm. to 40 mm., and the cat died within thirty minutes of injection. The blood-pressure of the control cat came down in the same time only from 160 mm. to 130 mm. It is further of interest to observe that the control cat absorbed 10 per cent. more β-i from the intestine than the bled cat, so that the latter cat was quickly killed by a smaller quantity of β-i than that which had but little effect on the control cat.

It can be said, therefore, that just as increasing the body fluids increases the resistance of the tissues, and more obviously of the medullary centres, to β-i, so also diminishing the body fluids by bleeding makes the same tissues extremely susceptible to β-i, so that the death of the animal quickly comes about.

I wish to point out again that the results here obtained cannot be applied completely to the more natural condition, from the point of view of this work, in which the body fluids are reduced by vomiting and diarrhoea, or when water is withheld from the diet.

An animal in this latter condition, with a large cellular and protein element of its blood, will undoubtedly be better able to render β-i innocuous than the bled animal, but I think it probable that, in both cases, the tissues of the body, and especially the respiratory centre, will have a reduced power of resisting that β-i which is not rendered innocuous.

I recognize it is difficult to dissociate the resistance of a tissue to a toxic substance and the power that tissue has of rendering a toxic substance innocuous ; for it seems evident that a substance only acts on a tissue in the inverse proportion to the power that the tissue has of rendering it innocuous by chemically transforming it. However, when a substance like β-i, which apparently kills by acting on a small part of the medulla oblongata, is being dealt with, I think it is permissible to discuss these two conditions as being, to some extent, independent. For the power the cells of the nervous system have of rendering a substance innocuous by causing a chemical transformation must be small compared with the liver and cellular elements of the blood. Consequently, I do not think there will be much difference in the resisting power of the medullary centres to β-i in the two types of animals deficient in blood, although the blood deficient in cellular elements will less efficiently make β-i absorbed from the intestine harmless than more normal blood.

Summary. In a bled animal, β-i absorbed from the intestine causes a more rapid fall in blood-pressure and the animal soon dies of respiratory failure.

(c) *Blood-pressure effects in fed animals.* It has been seen in previously described experiments that the absorption of water and food-stuffs depresses the rate of absorption of β-i from the intestine.

Considered from the point of view of blood-pressure, several interesting facts are revealed in the case of digesting animals. I do not here refer to the comparison of well-fed and starving animals, for experiments on this point have not been made. Incidentally, however, I may say that there is no doubt, from observation in well-fed and poorly conditioned animals, that the former can deal with large amounts of β-i and their blood-pressure be little depressed, while the latter die very readily and experience a rapid and marked fall of blood-pressure after absorbing small quantities of β-i. In comparative experiments such as comprise a large part of this work, this question regarding the state of nutrition has always been a difficulty, and can only be surmounted by keeping the animals for some days on a known diet before the experiment.

In the following experiments, diets of meat or milk or fat were given to cats at varying periods from one to six hours before being anaesthetized, and the effect on the blood-pressure produced by β-i absorbed from the intestine was observed.

1. *Meat.*

If the animal had eaten meat four hours or less before the injection of β-i into the intestine the results were too indefinite to be interpreted, for we have previously seen that the digestion and absorption of meat depresses slightly the absorption of β-i from the intestine. Consequently it is not surprising that the fall in blood-pressure in the meat-fed cat is not so pronounced in the majority of cases as in the control cat.

When the interval between eating the meat and injecting β-i is about six hours then the effect is more obvious, as can be seen in Experiment 139. Cat *B* was given 30 grm. of meat about seven hours before the β-i was injected into the intestine. Cat *A* was not given meat. It will be seen that the blood-pressure in *B* fell from 134 to 122 in the time that the blood-pressure in *A* (no meat) fell from 125 to 82. There was only 3 per cent. difference in the amount of β-i absorbed in these two cats, so that this could not explain the large difference in blood-pressure effect.

The increase in an animal's resistance to β-i produced by meat is clearly different from the increased resistance conferred on an animal by injecting a saline solution into the blood. In the former instance the blood-pressure is not allowed to be depressed to anything like the same degree as in the latter animal, although in both cases the blood-pressures recover and the animals survive. The entrance of the digestive products of the meat has a stimulating action on the cells of the body, giving them an increased metabolic power, so that the β-i is acted upon with greater readiness and more quickly made innocuous. In this change, the cells of the nervous system no doubt participate, and, as has been previously mentioned, if these cells can transform β-i more easily, then they will not be so susceptible to its toxic action.

Summary. When an animal has digested and absorbed a meal of meat the

depression of the blood-pressure caused by β-i absorbed from the intestine is considerably less marked than in a non-digesting animal. The animal has an increased capacity for chemically changing the β-i and making it harmless.

2. *Milk.*

The feeding of milk seems to have a similar effect to that of meat, but, in this case, the depression on the absorption of β-i from the intestine is more marked and the difference in the blood-pressure effect smaller, so that one can only say that the resistance of the tissues, although it is probably increased to some extent, is not so great as in the meat-fed animal.

3. *Fat.*

The results observed after feeding on fat are interesting. Of the experimental results quoted in the protocols, only one, Experiment 146, will be mentioned here, but it will be seen that they are all of the same nature. In Experiment 146 cat *B* ate 20 grm. of beef-fat 4¾ hours before the β-i was injected into the intestine. Cat *A* had no food. In cat *B* (fat) the blood-pressure came down quickly, after the β-i was injected, from 124 mm. to 98 mm., after which it rose steadily to 150 mm. In the control cat *A* the blood-pressure came down after injection from 160 mm. to 88 mm., and then steadily rose to an average of 115 mm. A similar subsequent rise of blood-pressure following a fall is seen in Experiment 95 on a fat-fed cat.

In a cat fed on fat the following blood-pressure effects are observed :

(1) The blood-pressure is only depressed to a small extent following the first absorption of β-i from the intestine.

(2) The blood-pressure afterwards rises to a point considerably higher than before the injection of β-i.

(3) After a certain period of time—often after the remarkably coincident time of one hour and forty minutes after the injection of β-i—the blood-pressure falls more or less suddenly, sometimes quite suddenly, and the animal dies.

A perusal of the amounts of β-i absorbed in these experiments compared to the results in the control animal will show that the fat-fed cats absorb less β-i than the control animals. The difference, however, is not sufficiently marked to explain the slight fall of blood-pressure in the fat-fed cats. For an explanation of this, it might appear at first sight that fat has a similar influence to the meat in previously described experiments, where it was thought that the meat had stimulated the tissues to have a greater metabolizing action on the absorbed β-i. I do not consider that this explanation will hold in the case of fat, for the reason that this would not explain why the cats should die suddenly after a certain length of time. Any explanation must certainly be able to cover this phenomenon, which, so far as my experiments have gone, seems fairly constant. I suggest that a reasonable explanation is offered along the following lines, although I have not yet been able to carry out the obvious experiment to prove it.

A substance can be absorbed from the intestine in two ways :

1. Via the blood-stream into the portal circulation.

2. Via the lacteals into the lymph and then into the blood.

Ordinary physiological teaching would lead one to expect that β-i would be absorbed only into the blood-stream and not into the lacteals. Now, in a fat-fed animal, the lacteals throughout the intestine, except probably for a few inches above the ileo-caecal valve, are full of fat, and if one looks at the mesentery when injecting β-i into a fat-fed animal one notices that the milkiness of the lacteals disappears in a minute or two. This probably means that the β-i solution is entering into the lymphatic circulation via the lacteals. What is the difference to the body between the β-i entering the blood via the lacteals and that which is directly absorbed into the blood? The difference is this: the β-i entering the portal blood has to pass through the liver, where a large part will probably be made innocuous, while the lymphatic absorbed β-i obtains access to all the tissues of the body without the possibility of being destroyed by the liver. In other words, portal-blood β-i may be innocuous, lymphatic β-i is probably toxic. Thus, if it should happen that the intestinal lymphatic system is full of fat, so that the lymph stream from the intestine is extremely slow, until the fat is removed from this position, the β-i entering the body from the intestine will have to pass into the portal circulation, and the liver can then deal with it and render it harmless. It would be expected that when the fat has been completely emptied out of the lymphatic channels into the blood-stream there would be a sudden flow of the lymph charged with β-i into the general circulation, and that this β-i would be extremely toxic. This suggestion would adequately explain why, in Experiment 146, the blood-pressure suddenly fell from 132 mm. to 50 mm., also in Experiment 96 from 130 mm. to 40 mm., in both cases the fall of pressure taking place 1 hour 40 minutes after the injection of β-i into the intestine. This phenomenon was also observed in all other cases, although the fall of pressure was not always instantaneous. It was at first thought to be due to the anaesthetic, for these fat-fed cats take an anaesthetic very badly, the smallest inhalation of ether or chloroform sending down the blood-pressure suddenly and killing them, unless great care is taken in the administration. Careful observation made it clear that the phenomenon was not related to the anaesthetic.

It is therefore concluded that the high blood-pressure met with in fat-fed cats, during the absorption of β-i from the intestine, is due to the fact that, owing to the temporary blocking up of the intestinal lymphatic system by fat, more of the absorbed β-i enters the body via the portal circulation, so that a large part of it is rendered innocuous by the liver before getting access to the central nervous system, the heart, and general circulation.

One fact the above suggestion does not adequately satisfy, viz. why the blood-pressure should go much higher when β-i is in the intestine than prior to its injection. At present I know no facts which explain this interesting phenomenon, and it seems useless to discuss it.

Summary. After a meal of fat, β-i absorbed from the intestine causes a slight fall in blood-pressure, followed by a rise to a point higher than that attained before any β-i is absorbed. This high pressure is retained for some

time—usually about $1\frac{3}{4}$ hours—and then falls more or less suddenly, and the animal dies of respiratory failure.[2]

XII.   *Summary of the Experimental Results with Animals.*

The most important results obtained in this research from a practical point of view, that is, results which seem to me to have a practical bearing on the subject of diarrhoea and vomiting of children, are as follows :

First, as regards the absorption of toxins like β-i from the intestine :

1. There is a marked delay in the absorption of toxic substances, normally in the intestine, when animals are injected with large quantities of fluid.

2. That water in the intestine delays the absorption of toxic substances.

3. That during the digestion of food-stuffs generally, meat, milk, sugar, and fat, there is a delay in the absorption of toxic substances.

4. That the presence of bile in the intestine delays the absorption of toxic substances.

5. That magnesium sulphate, of a concentration of 2 per cent. or over, delays the absorption of toxic substances from the intestine. A less concentration of $MgSO_4$ has no effect.

6. That morphine, below the point of being a serious menace to the respiratory centre, has no effect on the absorption of toxic substances.

Secondly, as regards the resisting power of the animal towards absorbed toxic substances :

1. The resistance of an animal against toxic substances is very greatly increased by the injection of fluid into the circulation.

2. An animal with a diminished amount of fluid, and particularly after the loss of a small amount of blood, has little power of resistance against toxic substances.

3. An animal's resistance is greatly increased after it has absorbed from the intestine food, and more particularly meat.

4. During the digestion of fat, toxic substances absorbed from the intestine have a diminished action, at least for some hours.

XIII.   *The Bearing of the above Results on the Aetiology of Diarrhoea and Vomiting.*

The research work I have described only allows me to discuss this subject from one point of view. I can pronounce no opinion on the important questions of differences of the bacteria, or superadded bacteria (microscopic or ultra-microscopic), or even the increase of chemical toxic substances in the intestine of diarrhoeic and vomiting children. At the same time my experimental

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[2] Since this paper was written some months ago, I have satisfied myself that the rise of blood-pressure following the fall is not so constant as earlier experiments led me to believe. Further, experiments made on lymphatic absorption of β-i from the intestine indicate that too little is absorbed in this way to explain the foregoing phenomena in the above manner.

results seem to indicate that given only the toxic products present in the
normal alimentary canal, together with a child reduced to such a condition
as that produced by an ordinary attack of diarrhoea and vomiting from any
dietetic indiscretion, these conditions alone can explain the serious results that
may follow.

What is the condition set up in a child suffering from an acute attack of
diarrhoea and vomiting? The primary cause of this condition I cannot discuss,
beyond saying that a child's alimentary canal is capable of being deranged by
many causes not necessarily bacterial in their nature.   Such a child has then—

1. No food in its alimentary canal and no water.

2. A deficiency of body fluids to a greater or less degree.

3. A loss of bile, including more particularly bile salts.

4. No reserves of absorbed food-stuffs in its whole economy.

These are precisely the conditions demonstrated in animal experiments for—

1. Allowing toxic substances to be absorbed from the alimentary canal
at a maximum rate.

2. Allowing the absorbed toxic substances to have their maximum effect.

It is thus clear that once the condition has been set up, the effects are
cumulative, for the diarrhoea and vomiting first produced allow substances
such as β-i to be absorbed, which by exerting their own action produce further
diarrhoea and vomiting and fall of blood-pressure and loss of fluid.   The child
becomes more and more susceptible, and death ultimately ensues.

Of these results the most important seems to me to be the loss of body
fluids.   The one condition associated with diarrhoea and vomiting which has
been regarded by clinicians as particularly prominent is the onset of this disease
in an epidemic form when the temperature of the air arrives and remains at
a certain high degree.   This temperature has constantly been regarded as
a causative factor in the production of bacterial products of a toxic nature and
it is supposed that these products are responsible for the epidemics.   All this
seems likely.   What I consider of greater importance, however, is that the high
temperature causes a great diminution of body fluids by evaporation, so that
when ordinary digestive derangement causing diarrhoea and vomiting is super-
added, the further loss of fluid, and other conditions described above, place the
child in the most susceptible state and deprive it of all power of resistance to
poisonous influences.

The body temperature of an animal is the result of a balance between heat
production and the loss of heat through radiation and conduction and loss by
evaporation.   The following figures obtained by Rubner show how the loss of heat
through evaporation becomes more important when the temperature is raised:

External Temperature.	Total Heat produced.	Loss by Conduction and Radiation.	Loss by Evaporation.
	Cal. per kg.	Cal.	Cal.
7·6° C.	83·5	71·7	11·8
15° C.	63·0	49·0	14·0
20° C.	53·5	37·3	16·2

These figures represent loss of heat in a dog, and it is seen how greatly the loss of heat by evaporation increases, especially when considered relatively to the loss by conduction and radiation. In a child the difference would be more striking, for the loss by evaporation forms normally a greater percentage of the heat loss:

	Loss of Heat. Radiation and Conduction.	Loss of Heat. Evaporation.
Man	77·1 %	22·9 %
Dog	79·5 %	20·5 %

It is evident, then, that a child is capable of losing a large percentage of its body fluids by normal evaporation during hot weather, so that when further loss of water by vomiting and diarrhoea is added, it will be seen how easily a child may enter the danger zone.

Apart from the experiments described in this research, it is well known from other facts, although to my mind it has never been fully appreciated, how susceptible the body is to loss of fluid. Arguing from the condition of the blood in cholera, Hill makes the remark that a fasting mammal can use up the whole of its body fat and 50 per cent. of its protein before dying, while a thirsting one becomes moribund when it has lost little more than 10 per cent. of its body fluids.

As for the draining away from the body of bile, and more especially the loss of bile salts, the fact that these substances inhibit the absorption of toxic substances from the intestine is important. I am inclined to think their importance is still greater for reasons I have not yet fully grasped. For instance, I think that bile salts, besides stimulating the liver to excrete bile, are also an effective stimulant to the liver cells, and enable them more completely to metabolize and render toxic substances innocuous.

To sum up:

1. A child suffering from diarrhoea and vomiting owing to loss of fluid, loss of bile salts, with an empty intestine and in a starving condition, is in an ideal position for allowing toxic substances normally present in the alimentary canal and mucous membrane to be rapidly absorbed and have their full toxic action.

2. That the association of this disease with a high atmospheric temperature in an epidemic form is to be explained largely by the additional loss of fluid due to evaporation of water, whereby the child keeps down its body temperature.

XIV. *The bearing of the Experimental Results on the Treatment of the Disease.*

At this point I wish to discuss the lines along which, according to my experimental results, such treatment ought to be directed. It seems proper, also, to point out here that the experimental conditions which form the basis of this work are artificial, and that it is impossible to say whether the deductions made from the results can be applied altogether to the treatment of

diarrhoea and vomiting of children. The fact that they are on the whole in close agreement with a recognized treatment of this disease, a treatment which has been evolved by empirical methods, makes one hope that they can be extended to clinical uses, and that, if they fail to cure, it is not because they are inherently wrong, but because in the disease there are other factors to be accounted for besides those studied, namely, the toxic action of substances absorbed from the alimentary canal. It is possible that there are other factors in the disease which have not been met in the experimental work, such, for instance, as a bacterial invasion of the blood or a deficiency in the body of chemical substances necessary for the sustenance of life. If this is the case, then such additional factors can only be discovered by combined experimental and clinical observation. For if the methods evolved from laboratory work, such as is here described, are radically inefficient when applied to the specific clinical cases, one can only assume that the experimental conditions do not sufficiently resemble the pathological state met with in the disease.

(a) *The necessity of increasing the body fluids to normal.* The first and fundamental line of treatment, according to the experimental results, is to raise the body fluids up to and beyond the normal amounts. The injection of fluid is, of course, a recognized treatment already used clinically, and the animal experiments above described only confirm this view and possibly place it on a more scientific basis. I wish to point out, however, more explicitly the importance of this measure. There are two things to remember: (1) That an animal with deficient body fluids has lost most of its power of resisting any toxic action; (2) that by increasing the body fluids well above the normal, the resistance to toxic action is greatly increased. From these facts it will be seen that, if a child continues to vomit everything, including water, then it is better to inject a sterilized saline solution into the blood-stream directly rather than subcutaneously. By injecting fluid into the blood-stream one can raise the body fluids well above the normal, but in subcutaneous injection the tissues seem to refuse to imbibe the fluid when a certain maximum is attained. Intravenous injection into a young infant with empty vessels is generally difficult and often impossible, and in these cases one is reduced to subcutaneous injection of salt solution.

As soon as vomiting subsides, even if only partially, the child should be given large quantities of fluid by mouth. To be given a few sips of water occasionally is of little value, and I do not consider it is possible to give too much water. As much as two ounces of water every hour should be given while the child is in a moribund condition, and until vomiting completely ceases. Water given by mouth and absorbed into the circulation from the alimentary canal is undoubtedly better than water injected in any other way. For it has been previously pointed out, that when water is in the intestine, the absorption of β-i, and no doubt other toxic substances present in the intestine, is more markedly diminished than when the body fluids are increased by the injection of salt solution into the blood. There is also evidence that when water is absorbed

through the alimentary mucous membrane it liberates substances capable of stimulating the organs of the body, such for example as the kidney, while water injected intraveneously or subcutaneously has no such action (11). Thus, for instance, it is said that water taken by mouth is a better diuretic than an equal quantity of water injected into the blood-stream, because in the former case a specific diuretic substance is liberated by the water from the mucous membrane of the alimentary canal which stimulates the kidney to activity. If this is true of renal activity, it seems probable that stimulants from other organs may also be liberated at the same time. All the evidence therefore points to the advisability of giving water by mouth to these children, if this is possible.

In order to administer a saline solution subcutaneously to a child the best plan is to place the sterile solution in a thermos flask, and to give it continuously in this way. Quantities of a pint, 568 c.c., can be injected in this way in a few hours, and this should be repeated until the child can take water by mouth.

It may be said, however, that if large quantities of fluid are injected intravenously into a child there may be a danger of producing oedema of the lungs. On this point my experience with children is not sufficiently great to speak with authority, but from a large experience with animals I should say there is but little danger so long as the child is not suffering from bronchitis and broncho-pneumonia. It is certainly true that, if anything has caused irritation to the lungs of cats, such for instance as the inhalation of ether or chloroform, and especially the former, oedema of the lungs is produced even when only small quantities of Ringer solution are injected into the blood. This is an important practical point and cannot be emphasized too strongly. I should say that treating shock on the operating table, after or during the inhalation of ordinary anaesthetics, by injecting salt solutions intravenously into a patient, may be a most dangerous proceeding in consequence of the ease with which oedematous lungs are produced after anaesthetics, especially after ether.

Broncho-pneumonia often develops as a terminal event in diarrhoea and vomiting of children, and in such cases intravenous injection of salt solution is contra-indicated, and more especially so, for by this time vomiting has usually disappeared, and it is possible for the child to retain water in its stomach.

In recent years a good deal of publicity has become attached to the ' sea-water ' treatment of diarrhoea and vomiting. In so far as, in this treatment, fluid is injected it must be of value, and I think it should be understood that it is the water that is the important element of this treatment. It is, of course, useful to have the fluid of a similar osmotic pressure and of somewhat similar constitution to the salt constituents of the tissues, but this is not an essential. It might be supposed that the magnesium element of the sea-water would be of importance, but my experimental results give no support to this view, and there is no doubt that normal salt solution or other physiological saline is quite as effective in the treatment of diarrhoea and vomiting of children as diluted sea-water.

(b) *Feeding*. The feeding of the child should start as soon as possible ; but, at the same time, it is useless to feed the child with any food requiring digestion so long as there is a deficiency of fluid in the body. This is obvious, for until the body fluids are normal, there will be no secretion of the digestive juices. The parched mouth of such children indicates the suppression of saliva, and the gastric juice has been observed to be similarly depressed. On the other hand, a large secretion of gastric juice can often be obtained by injecting saline into the blood-stream of an animal. If the secretion of gastric juice is absent, then all the other digestive juices of the pancreas and alimentary canal are suppressed, and in addition the absence of hydrochloric acid allows bacterial decomposition to develop to its fullest extent, so that food taken by mouth decomposes and a worse condition of sapraemia is produced. The custom of giving children albumin water at an early and severe stage of the disease seems to me to be contra-indicated in consequence of the decomposition-changes the albumin is liable to undergo in the absence of a secretion of proteolytic juices and hydrochloric acid. Speaking theoretically, I should say that a solution of 10 per cent. dextrose made up with 0·5 per cent. HCl would seem the most reasonable food-stuff to give the child. If this is retained, one might then pass on to a solution of whey containing a large proportion of lactose and so on to milk, the latter being diluted. The importance of feeding the child at as early a stage as possible is necessary, in order to afford some resistance to the tissues of the child in view of the sequelae, such as broncho-pneumonia, which intervene so frequently. After a child has had no nourishment for some days, it can offer no resistance to such a disease as broncho-pneumonia, and the possibility of this development must always cause one to remember the importance of supplying a source of energy as soon as possible.

I am aware that the administration of carbohydrates is regarded as bad treatment, but given with dilute hydrochloric acid, I cannot see any possibility of it doing harm, and if absorbed in the intestine, as I think it would be, it can only do good.

(c) *The use of purgatives*. My experimental work has afforded but little insight into the value of purgatives in diarrhoea and vomiting of children. It was seen that magnesium sulphate very efficiently retarded the absorption of β-i from the intestine in concentration above 2 per cent., but below this figure it had no effect. If this substance is used in treatment, therefore, it must be in fairly large doses to be at all effective. Here, again, it is useless to give such a drug until the body fluids are up to or above normal, and there is no doubt but that, the more fluid there is in the body, the better will $MgSO_4$ exert its cathartic action and suppress the absorption of toxic substances into the blood-stream.

Another substance which ought to be effective is castor oil, for we have seen that fats have a protecting action on the organism. If the fats of the oil are absorbed, their large caloric value must be very useful to children in this condition. Still recommends castor oil in 5 minim doses, and states that if thus given it has a constipating effect. One must assume that the oil in

these cases is not hydrolysed by the lipase of the pancreatic juice, and if this is so, the question arises as to whether it is absorbed from the alimentary canal. Whether calomel is a good purgative to give, I am unable to say. I should think there is always some danger in giving a substance like this, because of the possibility of absorption, and especially so when the body fluids are below normal, as in diarrhoea and vomiting. Calomel, when absorbed, like any other ionized mercurial compound, may have bad results.

(d) *The danger of morphine.* Standard clinical text-books on diarrhoea and vomiting of children teach that opium and morphine are very useful drugs in the treatment of this condition, especially when the alimentary canal is in a state of hyper-irritability, and there can be but little doubt that for suppressing the diarrhoea and vomiting, and generally reducing the movements of the alimentary canal, small doses of tinctura camphorae co. or Dover's powder, or tinct. opii, or even a hypodermic injection of morphine (although this latter has a preliminary effect of increasing vomiting) are excellent drugs. It is further stated in the same text-books how dangerous morphine can be if not used carefully and correctly. I have been most impressed in the animal experimental results above described by this fact. A cat is not very susceptible to morphine, and in order to produce Cheyne-Stokes breathing I have sometimes injected as much as 10 c.c. of liq. morphinae hydrochlor. into the circulation without causing death. In the above-described experiments, however, 5 minims injected into the alimentary canal were sufficient to bring about collapse of the respiratory centre, and death, when the animal was also absorbing β-i. It seems to me that, in a moribund and collapsed child, a most important point in treatment must be to avoid depressing in any way the respiratory centre, so that, although morphine is useful for suppressing the symptoms of diarrhoea and vomiting, I feel it should not be administered in this condition from any other point of view. In the amounts likely to be given to the child, it was seen above that it can have no action in suppressing the absorption of toxic substances from the alimentary canal.

Finally, of all treatment in this condition, the one thing essential is to get the volume of body fluids of the child back to normal or above normal, for otherwise—

1. The absorption of toxins from the intestine goes on at a maximum rate.

2. The absorbed toxic substances have their full toxic action and cannot be made harmless by the tissues to any marked extent.

3. All the digestive juices are suppressed and food only decomposes with the further production of toxins.

Protocols.

Note on Experiments.

The experimental procedure is fully explained in the text. In order to understand the following results, it may be stated briefly that the active substance β-i was placed in loops of intestine of 25 cm. length and left there for varying periods of time. Then the loops were removed and the contents washed out carefully with hot water, and made up to a volume of 300 c.c. In order to estimate the amount of β-i which had disappeared during the time of absorption, the power of the washings to contract a guinea-pig's uterus was compared with that of the original β-i solution. If, for instance, it took 0.5 c.c. of the experimental solution to contract the uterus to the same height as that produced by 0.25 c.c. of the original β-i solution, then it can be seen that 50 per cent. of the β-i placed in the intestine must have disappeared during its sojourn there.

A reading such as $0.2 \, \beta\text{-i} = 0.4 \, A_1 = 0.6 \, A_2$ means that 0.2 c.c. of the original β-i solution, 0.4 c.c. of the washings from the loop of intestine A_1, and 0.6 c.c. of the washings of loop A_2 all had a similar power of contracting the same uterus. Since these solutions were equal in strength at the beginning of the experiment, some of the β-i (50 per cent.) must have been absorbed from loop A_1, and more (66.6 per cent.) from A_2.

EXPERIMENT 71 (p. 171).
> Loop (2) at caecal end.
> Loop (1) taken 2 inches above loop (2).
> Mesenteric blood-vessels of loop (1) tied.
> 5 c.c. of a 1 per cent. solution of β-i placed in each loop.

Time of absorption :
> 2 hours 5 minutes.

Result :
> 0.3 c.c. of β-i = 0.3 c.c. loop (1) = 1 c.c. loop (2).

Amount of β-i absorbed :
> Loop (1) 0 per cent.
> Loop (2) 70 per cent.

EXPERIMENT 73 (p. 172).
> Two cats, A and B.
> Blood-vessels of 1 foot of jejunum tied in each.
> Two loops of each cat at caecal end injected with 5 c.c. of a 1 per cent. solution of β-i.

Time of absorption :
> A, 2 hours.
> B, 1 hour 45 minutes.

Result :
> 0.45 c.c. β-i = 0.85 c.c. A_1 = 1 c.c. A_2,
> $= 0.8$ c.c. B_1 = 0.9 c.c. B_2.

EXPERIMENT 52 (p. 172).
> Two cats, A and B.
> Two loops in each cat injected.
> Loops A_1 and B_1 at jejunal end of small intestine.
> Loops A_2 and B_2 at caecal „   „   „   „
> 5 c.c. of 1 per cent. solution of β-i injected into each loop.

Time of absorption :
> A, 2 hours 40 minutes.
> B, 2 hours 35 minutes.

Result:
$$0\cdot2 \text{ c.c. } \beta\text{-i} = 0\cdot4 \text{ c.c. } A_1 = 0\cdot6 \text{ c.c. } B_1,$$
$$= 1\cdot2 \text{ c.c. } A_2 = 1\cdot8 \text{ c.c. } B_2.$$

Amount of β-i absorbed:

$A_1 = 50$ per cent., $A_2 = 60$ per cent.

$B_1 = 84$ per cent., $B_2 = 90$ per cent.

EXPERIMENT 134 (p. 172).

Two cats, A and B.

Two loops in each cat injected.

Two loops, A_2 and B_2 at caecal end.

A_1 and B_1 25 cm. above loops A_2 and B_2 respectively.

5 c.c. β-i 1 per cent. solution injected into each loop.

Time of absorption:

A, 1 hour 17 minutes.

B, 1 hour 18 minutes.

Result:
$$0\cdot1 \text{ c.c. } \beta\text{-i solution} = 0\cdot2 \text{ c.c. } A_1 = 0\cdot22 \text{ c.c. } A_2,$$
$$= 0\cdot22 \text{ c.c. } B_1 = 0\cdot3 \text{ c.c. } B_2.$$

Amount of β-i absorbed:

$A_1 = 50$ per cent., $A_2 = 55$ per cent.

$B_1 = 55$ per cent., $B_2 = 66$ per cent.

EXPERIMENT 123 (p. 173).

A. C. E.

Two cats.

A. No food.

B. Given 100 c.c. milk by mouth $4\frac{1}{2}$ hours before β-i injected.

5 c.c. β-i 1 per cent. solution injected into loop of intestine at caecal end in each cat.

Time of absorption:

2 hours in each case.

Result:
$$0\cdot4 \text{ c.c. } \beta\text{-i} = 1\cdot2 \text{ c.c. } A = 0\cdot8 \text{ c.c. } B.$$

Amount of β-i absorbed:

A = 66 per cent.

B = 50 per cent.

EXPERIMENT 37 (p. 173).

Two cats.

A. No food.

B. Given milk by mouth $5\frac{1}{2}$ hours before β-i injected.

5 c.c. β-i 1 per cent. solution injected into three loops of each cat.

Time of absorption.

A, 4 hours.

B, 3 hours 50 minutes.

Result:
$$0\cdot5 \text{ c.c. } A_1 = 1 \text{ c.c. } A_2 = 1 \text{ c.c. } A_3 = 0\cdot2 \text{ c.c. } B_1 = 0\cdot2 \text{ c.c. } B_2 = 0\cdot6 \text{ c.c. } B_3.$$

Amount of β-i absorbed:

Original solution not estimated, but it is evident that much more β-i has been absorbed from the intestine of the unfed cat than from that of the fed one.

EXPERIMENT 125 (p. 173).

Two cats, A and B.

A. No food.

B. 30 grm. meat eaten 1 hour 50 minutes before β-i injected.

5 c.c. β-i 1 per cent. solution injected into 1 loop of intestine in each cat.

Time of absorption:
    $1\frac{1}{2}$ hours in each cat.
Result:
    0·35 c.c. β-i = 0·65 c.c. A_1 = 0·55 c.c. B_1.
Amount of β-i absorbed:
    A = 46 per cent.
    B = 36 per cent.

EXPERIMENT 129 (p. 173).
    Two cats, A and B.
    A. No food.
    B. 35 grm. meat $4\frac{1}{2}$ hours before β-i injected.
    Loops A_2 and B_2 at caecal end of intestine.
    Loops A_1 and B_1 25 cm. distance above loops A_2 and B_2 respectively.
    5 c.c. β-i 1 per cent. solution injected into each loop.
Time of absorption:
    $2\frac{1}{2}$ hours in each cat.
Result:
    0·1 c.c. β-i = 0·35 c.c. A_1 = 0·5 c.c. A_2,
                   = 0·35 c.c. B_1 = 0·35 c.c. B_2.
Amount absorbed:
    A_1 = 70 per cent., A_2 = 80 per cent. (control),
    B_1 = 70 per cent., B_2 = 70 per cent. (meat).

EXPERIMENT 145 (p. 173).
    Two cats.
    A. Given 20 grm. fat by mouth 6 hours before β-i injected.
    B. No food.
    Two loops in each cat injected—
        A_1 and B_1 at duodeno-jejunal flexure.
        A_2 and B_2 25 cm. distance above ileo-caecal valve.
    5 c.c. β-i 0·5 per cent. solution injected into each loop.
Time of absorption:
    1 hour in each cat.
Result:
    0·35 c.c. β-i = 0·55 c.c. A_1 = 0·5 c.c. A_2,
                     = 0·6 c.c. B_1 = 0·6 c.c. B_2.
Amount of β-i absorbed:
    A_1 = 36 per cent., A_2 = 30 per cent. (fat fed).
    B_1 = 42 per cent., B_2 = 42 per cent. (control).

EXPERIMENT 146 (p. 173).
    Cat A, no food.
    Cat B, 20 grm. fat $4\frac{1}{2}$ hours before injection.
    Loops A_2 and B_2 at caecal end.
    Loops A_1 and B_1 50 cm. above loops A_2 and B_2 respectively.
    Lacteals of B_1 and B_2 full of fat, especially B_1.
    5 c.c. β-i 0·5 per cent. solution injected into each loop.
Fat in lacteals of loops injected in cat B disappeared within 3 minutes of injection.
Time of absorption:
    A, 1 hour 50 minutes.
    B, 1 hour 50 minutes.
Result:
    0·4 c.c. β-i = 1·5 c.c. A_1 = 1·8 c.c. A_2,
                   = 1·2 c.c. B_1 = 1·5 c.c. B_2.

Amount of β-i *absorbed:*

$A_1 = 73$ per cent., $A_2 = 78$ per cent.

$B_1 = 66$ per cent., $B_2 = 73$ per cent.

EXPERIMENT 144 a (p. 174).

One cat.

Two loops injected.

Loop (2) at caecal end of intestine.

Loop (1) 25 cm. distance above loop (2).

Loop (1) contained 3 c.c. water + 5 c.c. β-i 1 per cent. solution.

„ (2) „ 3 c.c. olive-oil emulsion + 5 c.c. β-i 1 per cent. solution.

The water and olive oil were injected into the two loops respectively $\frac{1}{2}$ hour before the β-i solution.

Time of absorption:

1 hour 20 minutes.

Result:

0·12 c.c. β-i = 0.4 c.c. $A_1 = 0$·3 c.c. A_2.

Amount of β-i *absorbed:*

Loop $A_1 = 70$ per cent.

Loop $A_2 = 60$ per cent.

EXPERIMENT 144 b (p. 174).

Chloroform.

One cat—two loops injected.

Loop (2) at caecal end of intestine.

Loop (1) 25 cm. distant above loop (2).

Loop (1) contained 3 c.c. water and 5 c.c. β-i 1 per cent. solution.

Loop (2) „ olive oil emulsion and 5 c.c. β-i 1 per cent solution.

The water and olive oil were injected into the two loops respectively 3 minutes before β-i solution injected.

Time of absorption:

1 hour 45 minutes.

Result:

0·12 c.c. β-i = 0·6 c.c. $B_1 = 0$·3 c.c. B_2.

Amount of β-i *absorbed:*

$B_1 = 82$ per cent. (control).

$B_2 = 60$ per cent. (olive oil).

EXPERIMENT 130 (p. 174).

Cat A, nothing.

Cat B, 25 c.c. 10 per cent. dextrose into small intestine (duodenum tied to prevent regurgitation) $\frac{1}{4}$ hour before β-i injected.

Time of absorption:

A, 1 hour 30 minutes.

B, 1 hour 30 minutes.

Result:

0·175 c.c. β-i = 0·5 c.c. $A_1 = 0$·7 c.c. A_2,

= 0·3 c.c. $B_1 = 0$·4 c.c. B_2.

Amount absorbed:

$A_1 = 65$ per cent., $A_2 = 75$ per cent. (control).

$B_1 = 42$ per cent., $B_2 = 56$ per cent. (dextrose).

EXPERIMENT 57 (p. 174).

Two cats, A and B.

Two loops in each injected.

Loops A_1 and B_1 at jejunal end of intestine.

Loops A_2 and B_2 at caecal „ „

Cat A, 40 minutes before β-i solution injected into loops, 60 c.c. of Ringer solution were injected into intestine at duodeno-jejunal flexure.

Cat B, no Ringer injection.

5 c.c. β-i 1 per cent. solution injected into loops.

Time of absorption :

A died after 1 hour 40 minutes.

B killed after 1 hour 35 minutes (respiration nearly knocked out).

Result :

$$0.1 \text{ c.c. } \beta\text{-i} = 0.15 \text{ c.c. } A_1 = 0.15 \text{ c.c. } A_2,$$
$$0.2 \text{ c.c. } B_1 = 0.9 \text{ c.c. } B_2.$$

Amount of β-i absorbed :

$A_1 = 33$ per cent., $A_2 = 33$ per cent. (Ringer in intestine).

$B_1 = 50$ per cent., $B_2 = 89$ per cent. (no Ringer).

EXPERIMENT 58 (p. 174).

Two cats, A and B.

Two loops in each injected.

Loops A_1 and B_1 at jejunal end of small intestine.

Loops A_2 and B_2 at caecal ,, ,, ,,

Cat A, 25 c.c. Ringer solution injected into intestine between loops A_1 and A_2 5 minutes before β-i injection.

Cat B, no Ringer.

5 c.c. β-i 1 per cent. solution injected into all loops.

Time of absorption :

A killed after 2 hours 40 minutes.

B died after 2 hours 30 minutes.

Result :

$$0.3 \text{ c.c. } A_1 = 0.6 \text{ c.c. } A_2,$$
$$0.35 \text{ c.c. } B_1 = 1.4 \text{ c.c. } B_2. \quad \text{Original solution not estimated.}$$

Amount of β-i absorbed :

It is clear that more β-i has been absorbed from B_1 than A_1 and more from B_2 than A_2.

EXPERIMENT 105 (p. 175).

Three loops of cat's intestine injected.

Loop (3) at caecal end.

Loop (2) 25 cm. distance above loop (3).

Loop (1)   ,,   ,,   ,, (2).

Loop (1) 1 c.c. cat's own bile + 5 c.c. β-i 1 per cent. solution.

Loop (2) no bile   5 c.c. β-i   ,,   ,,   ,,

Loop (3) 1 c.c. cat's own bile + 5 c.c. β-i   ,,   ,,   ,,

Time of absorption :

2 hours 30 minutes.

Result :

1 c.c. β-i = 2 c.c. (1) = 3 c.c. (2) = 1.5 c.c. (3).

Amount of β-i absorbed :

Loop (1) 50 per cent., with bile.

Loop (2) 66 per cent., no bile.

Loop (3) 34 per cent , with bile.

EXPERIMENT 106 (p. 175).

One cat.

Two loops injected.

Loop (1) and loop (2) at caecal end, $\frac{1}{2}$ inch between each.

Loop (1) contained $\frac{1}{2}$ c.c. bile + 5 c.c. β-i 1 per cent. solution.

Loop (2) contained 5 c.c. β-i 1 per cent. only.

Time of absorption:
   2 hours 40 minutes.
Result:
   0·08 c.c. β-i = 0·2 c.c. A_1 = 0·8 c.c. A_2.
Amount of β-i absorbed:
   Loop (1) 60 per cent., with bile.
   Loop (2) 90 per cent., no bile.

EXPERIMENT 108 *a* (p. 175).   Bile duct tied.
   One cat.
   Loop (1) at jejunal end of small intestine.
   Loop (2) $\frac{1}{2}$ inch below loop (1).
   Loop (1) contained 5 c.c. β-i 1 per cent. solution.
   Loop (2)   „   „   „   „   „ $+\frac{1}{4}$ c.c. bile-salt solution.
   Bile-salt solution contained 6 per cent. sodium glycocholate,
                                          2 per cent. sodium taurocholate.
Time of absorption:
   2 hours 30 minutes.
Result:
   0·6 c.c. loop (1) = 0·5 c.c. loop (2).
Amount of β-i absorbed:
   β-i solution was not estimated, and therefore it is not possible to say how
much was absorbed.
   It is clear, however, that more was absorbed from loop (1), which contained
no bile salts.

EXPERIMENT 108 *b* (p. 175).   Bile duct tied.
   One cat.
   Loop (2) at caecal end of intestine.
   Loop (1) $\frac{1}{2}$ inch above loop (2).
   Loop (1) contained 5 c.c. β-i 1 per cent. solution.
   Loop (2)   „   „   „   „   „ $+\frac{1}{4}$ c.c. bile-salt solution.
   Bile-salt solution contained 6 per cent. sodium glycolate,
                                          2 per cent. sodium taurocholate.
Time of absorption:
   2 hours 30 minutes.
Result:
   1·7 c.c. loop (1) = 0·7 c.c. loop (2).

EXPERIMENT 137 (p. 176).
   One cat.
   Two loops injected.   Loop (2) at caecal end of intestine.
                         Loop (1) 25 cm. distance above loop (2).
   Loop (1) contained 2 c.c. water + 5 c.c. 0·5 per cent. β-i solution.
   Loop (2) contained 2 c.c. 20 per cent. $MgSO_4$ + 5 cc. β-i 0·5 per cent. solution.
Time of absorption:
   2 hours.
Result:
   0·35 c.c. β-i = 0·8 c.c. loop (1) = 0·5 c.c. loop (2).
Amount absorbed:
   Loop (1) 56 per cent.
   Loop (2) 30 per cent.

EXPERIMENT 138 (p. 177).
   Two cats, A and B.
   Two loops of each injected. A_2 and B_2 at caecal end of intestine; A_1
and B_1 25 cm. distance above A_2 and B_2.

A_1 contained 5 c.c. β-i 0·5 per cent. solution + 2 c.c. 20 per cent. $MgSO_4$.
A_2 „   „   „   „   „   + 2 c.c. water.
B_1 „   „   „   „   „   + 2 c.c. water.
B_2 „   „   „   „   „   + 2   „   „

The $MgSO_4$ solution and the water were injected into the loops about 3 minutes before the β-i solution.

Time of absorption :
    A, 2 hours.
    B, 2 hours.
Result :
    0·4 c.c. β-i = 0·6 c.c. A_1 = 1·7 c.c. A_2,
                    = 1·2 c.c. B_1 = 1·3 c.c. B_2.
Amount absorbed :
    A_1 = 33 per cent., A_2 = 76 per cent.
    B_1 = 66 per cent., B_2 = 69 per cent.

EXPERIMENT 136 (p. 177).
    Two cats, A and B.
    Loops A_1 and B_1 at jejunal end of small intestine.
    Loops A_2 and B_2 at caecal   „   „   „
    Loop A_1 contained 1 c.c. water + 5 c.c. β-i 1 per cent. solution.
    Loop A_2 „   „   +   „   „   „
    Loop B_1 „   „   +   „   „   „
    Loop B_2 contained 1 c.c. $MgSO_4$ 5 per cent. solution + 5 c.c. β-i (i.e. 0·83 per cent. $MgSO_4$).
Time of absorption :
    A, 1 hour 48 minutes.
    B, 1 hour 22 minutes.
Result :
    0·25 c.c. β-i = 0·3 c.c. A_1 = 0·5 c.c. A_2,
                     = 0·5 c.c. B_1 = 0·6 c.c. B_2.
Amount absorbed :
    A_1 = 17 per cent.
    A_2 = 50 per cent.
    B_1 = 50 per cent.
    B_2 = 58 per cent. $MgSO_4$ loop 0·83 per cent.

EXPERIMENT 134 (p. 177).
    Two cats, A and B. β-i injected into two loops of each.
    A_2 and B_2 at caecal end of small intestine.
    A_1 and B_1 25 cm. distance above A_2 and B_2.
    Into each loop, A_1, A_2, B_1, and B_2, 5 c.c. β-i 1 per cent. solution were injected.
    Between loops A_1 and A_2, 5 minims of liq. morph. hydrochlor. were also injected.
    Into B, no morphia.
Time of absorption :
    A, 1 hour 18 minutes (died), morphine.
    B, 1 hour 18 minutes (killed), no morphine.
Result :
    0·1 c.c. β-i = 0·2 c.c. A_1 = 0·22 c.c. A_2,
                    = 0·22 c.c. B_1 = 0·3 c.c. B_2.
Amount of β-i absorbed by each loop.
    A_1 = 50 per cent., A_2 = 55 per cent., morphine.
    B_1 = 55 per cent., B_2 = 66 per cent., no morphine.

EXPERIMENT 133 *b* (p. 178).

One cat.

Two loops were injected with 5 c.c. β-i 1 per cent. solution.

Loop (2) at caecal end.

Loop (1) 25 cm. distance above loop (2).

1 c.c. of liq. morphinae hydrochlor. was injected into the intestine above loop (1).

Time of absorption:

1 hour 10 minutes.

During the last 40 minutes, the respiratory centre worked badly, after which the cat died of respiratory failure.

Result:

0·375 c.c. β-i = 0·6 c.c. loop (1) = 0·625 c.c. loop (2).

Amount of β-i absorbed by the loops of intestine:

Loop (1) 37·5 per cent.

Loop (2) 40·0 per cent.

EXPERIMENT 133 *a* (p. 179).

Two loops at caecal end injected with β-i 1 per cent. solution.

Loop (2) at caecal end.

Loop (1) 25 cm. distance above loop (2).

Loop (1) contained 5 c.c. β-i 1 per cent. solution + 1 c.c. of water.

Loop (2)   ,,   ,,   ,,   ,,   + 1 c.c. 5 per cent. Na_2CO_3.

Time of absorption:

2 hours 30 minutes.

Result:

0·375 c.c. β-i = 1 c.c. loop (1) = 1·2 c.c. loop (2).

Amount absorbed:

Loop (1) 62·5 per cent.

Loop (2) 69·0 per cent.

EXPERIMENT 120 (p. 178).

Alkali at jejunal end of small intestine.

Two loops injected with 5 c.c. β-i 0·5 per cent. solution.

Loop (1) at duodeno-jejunal flexure.

Loop (2) immediately below loop (1).

Loop (1) contained 1 c.c. of 5 per cent. Na_2CO_3 in addition to the β-i solution.

Time of absorption:

2 hours 34 minutes.

Result:

0·3 c.c. β-i = 1·7 c.c. loop (1) = 0·6 c.c. loop (2).

Amount absorbed:

Loop (1) 82 per cent.

Loop (2) 50 per cent.

EXPERIMENT 140 (p. 180).

Two cats, A and B.   A much larger than B.

Two loops of intestine injected with 5 c.c. β-i 1 per cent. solution.

A_2 and B_2 loops at caecal end of intestine.

A_1 and B_1 25 cm. above A_2 and B_2.

From A, 23 c.c. blood withdrawn from carotid 4 minutes before β-i injected.

B, 17   ,,   ,,   ,,   ,,   ,,   19   ,,   after   ,,   ,,

Time of absorption:

A, 2 hours.

B, 2 hours.

Result:

0·2 c.c. β-i = 0·4 c.c. A_1 = 0·6 c.c. A_2,

= 0·8 c.c. B_1 = 0·1 c.c. B_2.

Amount of β-i absorbed:

   $A_1 = 50$ per cent., $A_2 = 66$ per cent., blood withdrawn.
   $B_1 = 75$ per cent., $B_2 = 80$ per cent., normal.
   A did not die in this case, but whereas the fall in blood-pressure in B was only 40 mm. Hg, in A it fell 68 mm. Hg.
   In other words, A. was much more affected by the smaller amount of β-i absorbed.

EXPERIMENT 141 (p. 180).

   Two loops of each cat injected with 5 c.c. β-i 1 per cent. solution.
   Loops A_2 and B_2 were at caecal end of small intestine.
   Loops A_1 and B_1 were 25 c.m. distance above A_2 and B_2.
   From A, 15 c.c. blood were withdrawn 3 minutes before β-i was injected.
      B, normal.

Time of absorption:

   A, 30 minutes, died.
   B, 30 minutes, lived.

Result:

   0.2 c.c. β-i = 0.25 c.c. A_1 = 0.3 c.c. A_2,
                 = 0.3 c.c. B_1 = 0.325 c.c. B_2.

Amount of β-i absorbed:

   $A_1 = 20$ per cent., $A_2 = 33$ per cent. (bled cat), died.
   $B_1 = 33$ per cent., $B_2 = 39$ per cent. (normal cat).
   In A, the blood-pressure fell rapidly from 90 to 48 mm. Hg.
   In B,   „   „   „   only from 160 to 138 mm. Hg.

EXPERIMENT 56 (p. 181).

   Cat B, bled 30 c.c. before injecting two loops of intestine with 5 c.c. β-i 1 per cent. solution each.
      Injected 2.25 p.m. }
      Died   2.40 p.m. } 15 minutes.
   Cat C, bled 20 c.c. before injecting β-i into intestine.
      Injected with β-i at 5.40 p.m. }
      Died   5.50 p.m. } 10 minutes.
   Cat A, control, i.e. not bled.
      Injected 2.20 p.m.
      Died   5.45 p.m., i.e., not till 3 hours 15 minutes had elapsed.

EXPERIMENT 50 (p. 182).

   Two loops of each cat injected with 5 c.c. β-i 1 per cent. solution.
   Loops A_2 and B_2 at caecal end of intestine.
   Loops A_1 and B_1 at jejunal end   „
   Into A 200 c.c. Ringer were injected into external jugular vein at 3.50 p.m.
         100   „   „   „   „   „   „   4.40 p.m.
         100   „   „   „   „   „   „   5.50 p.m.

Time of absorption:

   A injected with β-i solution, 4.30 p.m.   B injected with β-i, 4.25 p.m.
   A killed   6.20 p.m.   B killed   6.20 p.m.

Result:

   0.15 c.c. β-i = 0.2 c.c. A_1 = 0.23 c.c. A_2,
                 = 0.25 c.c. B_1 = 0.5 c.c. B_2.

Amount of β-i absorbed:

   $A_1 = 25$ per cent., $A_2 = 35$ per cent., Ringer.
   $B_1 = 40$ per cent., $B_2 = 70$ per cent., without Ringer.

EXPERIMENT 52 (p. 182).

   Two loops of intestine in each cat injected with 5 c.c. β-i 1 per cent. solution.
   Loops A_1 and B_1 at jejunal end of intestine.
   Loops A_2 and B_2 at caecal   „   „

Ringer injected into external jugular vein of A 200 c.c. at 11.10 a.m.
100 c.c. at 11.45 a.m.
100 c.c. at 12.45 p.m.
100 c.c. at 2.10 p.m.

Time of absorption:

A injected with β-i, 11.40 a.m.   B injected with β-i, 11.35 a.m.
A killed   2.20 p.m.   B died   2.10 a.m.

Result:

0·2 c.c. of β-i = 0·4 c.c. A_1 = 1·2 c.c. A_2,
= 0·6 c.c. B_1 = 1·8 c.c. B_2.

Amount of β-i absorbed:

A_1 = 50 per cent., A_2 = 82 per cent., with Ringer.
B_1 = 66 per cent., B_2 = 89 per cent., no Ringer.

EXPERIMENT 110 (p. 182).

Two loops of intestine in each cat.
All the loops at caecal end of intestine.
Into A, 10 c.c. of Ringer solution were injected at intervals of about 15 minutes from 2.20 to 5 p.m.
B no Ringer.

Time of absorption:

A injected with β-i, 2.25 p.m.   B injected, 2.40 p.m.
A killed   5.2 p.m.   B died   5.2 p.m.

Result:

0·4 c.c. β-i = 0·8 c.c. A_1 = 1·5 c.c. A_2,
= 2·0 c.c. B_1 = 2·5 c.c. B_2.

Amount of β-i absorbed:

A_1 = 50 per cent., A_2 = 73 per cent., Ringer.
B_1 = 80 per cent., B_2 = 84 per cent., no Ringer.

EXPERIMENT 143 (p. 183).

5 c.c. β-i 1 per cent. solution were injected into two loops in each cat, A and B.
Loops A_2 and B_2 at caecal end of intestine.
Loops A_1 and B_1 25 cm. distance above A_2 and B_2.
In B, at 11.45 p.m., 25 c.c. of 100 per cent. solution of dextrose were injected into the external jugular vein.
A no dextrose.

A, β-i injected 11.50 p.m.   B, β-i injected 11.45 p.m.
A killed   12.54 p.m.   B died   12.47 p.m.

Result:

0·25 c.c. β-i = 0·4 c.c. A_1 = 0·45 c.c. A_2,
= 0·45 c.c. B_1 = 0·7 c.c. B_2.

Amount of β-i absorbed:

A_2 = 37 per cent., A_2 = 55 per cent. (control).
B_1 = 55 per cent., B_2 = 64 per cent. (dextrose).

EXPERIMENT 115 (p. 184).

Two loops of each cat (A and B) injected with 5 c.c. β-i 1 per cent. solution.
Loops A_2 and B_2 at caecal end.
Loops A_1 and B_1 25 cm. distance above loops A_2 and B_2 respectively.
Ringer solution containing 0·5 per cent. $MgSO_4$ was injected into the external jugular vein of B as follows:

25 c.c. of solution at 3.2 p.m.
25   „   „   „   3.32 p.m.

A, β-i injected 2.40 p.m.   B, β-i injected 3.10 p.m.
A died   3.45 p.m.   B killed   4.15 p.m.

Result:

0·35 c.c. β-i = 0·75 c.c. A_1 = 0·7 c.c. A_2 (control),
= 0·75 c.c. B_1 = 1·3 c.c. B_2 ($MgSO_4$).

Amount of β-i absorbed:
$A_1 = 53$ per cent., $A_2 = 50$ per cent. (control).
$B_1 = 53$ per cent., $B_1 = 73$ per cent. $(MgSO_4)$.

EXPERIMENT 47 (p. 184).
5 c.c. of β-i 1 per cent. solution, were injected into two loops of each cat (A and B).
Loops A_1 and B_1 were at the jejunal end of small intestine.
Loops A_2 and B_2 „   „   caecal   „   „   „
Secretin was made in the ordinary way from the mucous membrane of the duodenum of another cat and injected into A as follows :

30 c.c. of secretin into A at 2.25 p.m.
15   „   „   „   2.57 p.m.
15   „   „   „   3.30 p.m.
15   „   „   „   4.0 p.m.
15   „   „   „   4.45 p.m.
15   „   „   „   5.15 p.m.

A, β-i injected 2.55 p.m.   B, β-i injected 2.45 p.m.
A killed   5.55 p.m.   B died   5.0 p.m.

Result :
0·2 c.c. β-i = 1   c.c. $A_1 = 1$ c.c. A_2,
      = 1·2 c.c. $B_1 = 0.8$ c.c. B_2.
Amount of β-i absorbed :
$A_1 = 80$ per cent., $A_2 = 80$ per cent., secretin.
$B_1 = 83$ per cent., $B_2 = 75$ per cent., no secretin.

EXPERIMENT 71 (p. 185).
5 c.c. β-i 1 per cent. solution injected into two loops.
Loop (1) at caecal end of small intestine.
Loop (2) including all large intestine.
β-i injected 3.40 p.m.
Cat died   5.35 p.m.
Result :
0·3 c.c. β-i = 0·5 c.c. $B_1 = 0.3$ c.c. B_2.
Amount of β-i absorbed :
$B_1 = 40$ per cent.
B_2 = none.

EXPERIMENT 132 (p. 185).
Three loops of intestine injected with 5 c.c. β-i 1 per cent. solution.
Loop (1) 25 cm. distance above loop (2).
Loop (2) just above ileo-caecal valve.
Loop (3) large intestine.
β-i injected 2.45 p.m.
Cat died   4.50 p.m.
Result :
0·15 c.c. β-i = 0·3 c.c. (1) = 0·3 c.c. (2) = 0·22 c.c. (3).
Amount of β-i absorbed :
Loop (1) = 50 per cent.
Loop (2) = 50 per cent.
Loop (3) = 30 per cent., large intestine.

EXPERIMENT 144 c (p. 185).
5 c.c. of a 1 per cent. β-i solution were injected into a loop of the large intestine, the mesentery of which was tied to prevent absorption.
Time of absorption : 2 hours 20 minutes.
Result : 0·4 c.c. β-i = 0·6 c.c. of loop contents.
Amount disappeared : 33 per cent.

EXPERIMENT 110 (p. 189).

Two cats.

A, Ringer injected in 10 c.c.
at intervals of 10 minutes.
110 c.c. injected altogether.

Blood-pressure A.
Before injecting β-i.
2.21 p.m. 110 mm. Hg.
After injection.
2.27 p.m. 64 mm. Hg.
2.43 „ 60 „
3.0 „ 64 „
3.20 „ 58 „
3.50 „ 62 „
4.10 „ 68 „
4.30 „ 67 „
4.55 „ 86 „
and up to 100 mm.

Amount of β-i *absorbed :*
A = 61 per cent.
B = 82 per cent.

B, no Ringer injected.

Blood-pressure B.
Before injecting β-i.
2.25 p.m. 120 mm. Hg.
After injection.
2.45 p.m. 70 mm. Hg.
3.0 „ 76 „
3.20 „ 84 „
3.50 „ 78 „
4.10 „ 74 „
4.30 „ 75 „
4.55 „ 64 „
and lower till death at 5 p.m.

EXPERIMENT 141 (p. 191).

A, 15 c.c. blood withdrawn
from carotid artery, 12.39 p.m.
β-i injected 12.42 p.m.
Blood-pressure.
Before injection.
12.40 p.m. 90 mm. Hg.
After injection.
12.50 p.m. 66 mm. Hg.
12.55 „ 48 „
down to 40 „
and died 1.10 p.m.

B, normal.

β-i injected 12.48 p.m.
Blood-pressure.
Before injection.
12.32 p.m. 160 mm. Hg.
After injection.
12.51 p.m. 138 mm. Hg.
1.0 „ 130 „
and remained so.
killed 1.16 p.m.

In the bled cat the blood-pressure came straight down to 48 mm., the control cat being very little affected. Yet the control cat absorbed 10 per cent. more β-i than the bled cat in the same period.

EXPERIMENT 139 (p. 192).

A, no food.
β-i injected 2.50 p.m.
Blood-pressure.
Before injection.
2.47 p.m. 125 mm. Hg.
After injection.
2.59 p.m. 106 mm. Hg.
3.10 „ 96 „
3.20 „ 82 „
3.40 „ 90 „
4.0 „ 96 „
4.25 „ 102 „
4.45 „ 124 „

B, given 30 grm. of meat at 8.0 a.m.
β-i injected 2.53 p.m.
Blood-pressure.
Before injection.
2.52 p.m. 134 mm. Hg.
After injection.
3.0 p.m. 115 mm. Hg.
3.10 „ 122 „
3.20 „ 122 „
3.35 „ 123 „
3.47 „ 120 „
4.12 „ 125 „
4.45 „ 150 „
4.53 „ 150 „

Amount of β-i absorbed:
$A_1 = 50$ per cent., $B_1 = 50$ per cent.
$A_2 = 73$ per cent., $B_2 = 66$ per cent.

EXPERIMENT 146 (p. 193).

A, no food.	B, 20 grm. of fat at 11 a.m.
β-i injected 3.45 p.m.	β-i injected 3.48 p.m.
Killed 5.34 p.m.	Killed 5.37 p.m.
Blood-pressure.	*Blood-pressure.*
Before injection of β-i.	Before injection of β-i.
3.40 p.m. 160 mm. Hg.	3.40 p.m. 124 mm. Hg.
After injection.	After injection.
3.53 p.m. 128 mm. Hg.	3.53 p.m. 98 mm. Hg.
3.57 „ 94 „	3.57 „ 112 „
4.7 „ 88 „	4.7 „ 140 „
4.20 „ 104 „	4.20 „ 146 „
4.35 „ 115 „	4.35 „ 144 „
4.50 „ 110 „	4.50 „ 150 „
5.0 „ 112 „	5.0 „ 132 „
5.20 „ 119 „	5.20 „ suddenly down to 50.
5.30 „ 128 „	

Amount of β-i absorbed:
$A_1 = 73$ per cent., $A_2 = 78$ per cent., no fat.
$B_1 = 66$ per cent., $B_2 = 73$ per cent., fat.

EXPERIMENT 95 (p. 193).

A, fat eaten 11.15 a.m.	B, no food.
Injected with β-i at 2 p.m.	Injected with β-i at 2.30 p.m.
Blood-pressure.	*Blood-pressure.*
Before injection.	Before injection.
1.55 p.m. 90 mm. Hg.	2.25 p.m. 135 mm. Hg.
After injection.	After injection.
2.7 p.m. 110 mm. Hg.	3.7 p.m. 122 mm. Hg.
3.10 „ 134 „	3.30 „ 100 „
3.30 „ 140 „	3.35 „ 78 „
3.55 „ 116 „	4.0 „ 90 „
	4.15 „ 84 „
	4.30 „ 82 „

Amount of β-i absorbed:
$A_1 = 50$ per cent., $A_2 = 33$ per cent.
$B_1 = 50$ per cent., $B_2 = 50$ per cent.

EXPERIMENT 145 (p. 193).

A, given 20 grm. of fat at 11 a.m.	B, no food.
β-i injected 4.47 p.m.	β-i injected 4.53.
Blood-pressure.	*Blood-pressure.*
Before injection.	Before injection.
4.36 p.m. 110 mm. Hg.	4.50 p.m. 120 mm. Hg.
4.45 „ 150 „	After injection.
After injection.	4.57 p.m. 76 mm. Hg.
4.57 p.m. 150 mm. Hg.	5.15 „ 68 „
5.30 „ 140 „	5.30 „ 72 „
5.42 „ 138 „	5.44 „ 76 „

Amount of β-i absorbed:
Loops $A_1 = 23$ per cent., $A_2 = 23$ per cent.
Loops $B_1 = 33$ per cent., $B_2 = 38$ per cent.

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THE QUANTITATIVE DETERMINATION OF AMYLASE IN BLOOD-SERUM AND URINE AS AN AID TO DIAGNOSIS [1]

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Introduction.

THE presence of a diastatic or amylolytic ferment in the urine and in the blood has long been known. Cohnheim (1) in 1863 I believe to have first observed its presence in the urine and made a record of the fact.

In 1867 Michael Foster (17) confirmed the presence of the ferment, and separated from the urine a strongly amylolytic fluid giving no proteid reaction. He also proved human blood to be amylolytic. He was unable to find any increase in amylolytic power in the blood or urine of diabetics.

But although the ferment was known to be present, it is only very recently that its study has been of any practical value. This is due to the fact that only of recent years has the estimation of ferments been carried out with any degree of accuracy, and the methods used by the early observers could only detect extremes of variation in either direction. Moreover, their methods were such that comparison of the results arrived at by different methods proved of no value. For this reason I propose to review only the modern literature on the subject.

When Oppenheimer (2) and others introduced modern methods of ferment estimation, many attempts were made to apply these to the determination of diastase in the urine for clinical purposes. J. Wohlgemuth (3), of the Charité, Berlin, was the first to solve the problem successfully, and his method still stands as the most useful.

The method, which he improved upon later, and made more delicate, was published in his *Methode zur quantitativen Bestimmung des diastatischen Ferments*, and was based on the use of iodine to detect the presence of undigested starch.

G. Moeckel and Rost (4) published another method in 1910, which is based on much the same principle of Wohlgemuth's, and has been used by them chiefly for estimation of the ferment in the blood-serum. Their method consists in

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estimating by titration, according to Bertrand's method, the amount of sugar split off from starch by the ferment.

In order to carry this out it is necessary, after digesting the starch solution with the serum, to clear the mixture of albumin (by the use of dialysed iron oxide) before titrating for sugar. The method is, therefore, much more complicated than Wohlgemuth's, and besides this there is a danger of error due to sugar already present in the serum. In the case of urine, except the urine of albuminuria, the process of removing albumin is of course not necessary.

The advantage of Moeckel and Rost's method is, of course, that it estimates the amount of end product of the ferment's action, rather than the amount of starch attacked by the ferment, but I think this possible gain in accuracy to be outweighed by the disadvantages of the method as compared with Wohlgemuth's.

In his original article, Wohlgemuth dealt chiefly with the amount of diastase in the urine of animals and men.

After tying the duct of the pancreas in a dog, he found, both in the urine and the blood, an increased amount of the ferment, which, however, very rapidly became normal again. He obtained the same result by ligaturing the ductus choledochus of the dog, but in this case the rise in value of the diastase occurred only after a few days, and was transient, which phenomenon Wohlgemuth explained by scar-formation in the duct of Wirsung.

Wohlgemuth (3) pursued this line of investigation no further, but experimenting on human urine, he found in four cases of nephritis, and two cases of diabetes, a subnormal level of the ferment. He, therefore, devoted two further papers to the value of diastase estimation as a test for renal efficiency, and proved it to be as valuable as the indigo-carmine, phloridzin, and other tests.

v. Benczur (5), working with Wohlgemuth's original method, examined the serum and urine of fifty cases, and found variations too great to be of value. In one case of occlusion of the pancreatic duct, however, he found a diastatic content much above normal, and he also found a high content in nine out of sixteen cases of nephritis and albuminuria. In all other cases, including diabetes, he found normal values.

Wynhausen (6), on the other hand, found in the urine of forty diabetics, and thirty-two cases of nephritis, a large decrease in diastatic content. This decrease he found in his case of diabetes to vary in proportion to the severity of the disease, so that he ascribed to the method a great prognostic value.

Hirschberg (7), using the method of Wohlgemuth, found an increase of diastase in the urine in some inflammatory conditions of the pancreas.

Marino (8), using a modified method of his own, found a great diminution of diastase in urine of pernicious and secondary anaemia.

Rosenthal (9), using the modified Wohlgemuth's method to be described later, found a decreased excretion of the ferment in diabetes and nephritis, whilst in some cases of increased permeability of the kidneys, and in infectious diseases, he found an increase.

Schaumberg obtained similar results in nephritis with a method devised by Müller, which consisted in allowing a drop of urine, or diluted urine, to work on a plate spread with the starch substratum, in the same way that gelatin plates are used for trypsin estimation, a method much inferior to Wohlgemuth's.

The investigations which follow arose from an attempt to test pancreatic efficiency, with a view to diagnosis of carcinoma of that organ, for one cannot help being struck with the frequency of cases of carcinoma of the stomach and liver, but especially of the former, which have their primary location in the head of the pancreas. I therefore sought for a reliable method of testing the functional activity of the pancreas. The Cammidge (10) Reaction was found to give most inconstant results. Einhorn's (11) bullet-tube method of obtaining duodenal content was not at my disposal, nor was Volhard's (12) cream or oil breakfasts, for the latter is impossible with English patients. A few tests with Schmidt's (13) silk sacs containing muscle fibre proved that this method was not to be relied upon, and the same seemed to be true of Sahli's (14) glutoid capsule method. This is not surprising, since these tests can be affected by factors beyond our control, and appear to be founded on principles which are not fixed or reliable. There is little reason to believe the finding of salicylic acid in the urine after a period of delay, in Sahli's method, is a sound indication for or against active pancreatic secretion. I therefore turned my attention to estimation of the pancreatic secretion by a direct method. This secretion, of course, consists chiefly of three ferments, trypsin, steapsin or lipase, and diastase or amylase, which enter the duodenum by the ducts of Wirsung and Santorini. One at least of these, trypsin, only becomes activated by the succus entericus.

Trypsin was therefore tested for in the faeces by Gross's (15) method, which consists in allowing a faintly alkaline solution of faeces to act on a casein solution, and testing for the end result with dilute acetic acid. Quantitative estimation by this method proved very difficult, and anything approaching accuracy could only be obtained by taking the average of a few days' results. There was also difficulty through the impossibility of preventing the growth of B. prodigiosus, which of course contains a proteolytic ferment.

Erepsin, secreted by the intestinal mucous membrane, also acts on casein, but is said to have no action on fibrin : the latter was not tried.

In spite of its disadvantages, however, provided that such factors as diarrhoea can be eliminated, Gross's method is invaluable as a means of estimating whether trypsin is present or absent in the faeces, or largely decreased, but as a quantitative method of measuring smaller variations in pancreatic efficiency, the method had to be abandoned.

Lipase and amylase then remained. Of these lipase has been estimated successfully by allowing an exactly neutralized solution of faeces to act upon a fat such as olive oil or mono-butyrin, and estimating the fatty acids set free by titration. The amount of lipase has been found by these observers, however, to be so variable that no reliable standard can be fixed even for health.

Amylase was then estimated by a method which proved simpler than any of the others, and was found to be present in all the cases examined. Moreover, the intestinal mucous membrane probably produces practically no amylase, so that its presence in the faeces means an entry of pancreatic juice into the intestinal canal, since presumably the amylolytic ferment of the saliva is destroyed in the stomach.

Turning now to the urine, some very interesting results have been obtained by other observers by estimating pepsinogen as an index of gastric activity; an attempt was therefore made to estimate pancreatic secretion in the same way.

Trypsin, though it is probably the most important of the pancreatic ferments, cannot be demonstrated in any amount in the urine, and then only by a very complex method. This may perhaps be due to a combination of the ferment with an antibody to produce a body resembling a pro-ferment. The necessity for such a linking is well demonstrated by the autolysis and peritonitis which occur when the ferment is set free by an acute pancreatitis. At any rate free trypsin, if present at all in the urine, appears to be only present in minute amounts.

Lipase may be demonstrated and estimated in the urine by a method similar to that used for faeces; but, as might be expected from the complexity of the processes involved, and the presence of fat as a rapidly varying constituent of normal blood, Abderhalden and others find great variations in the amount of this ferment in the urine and blood, with apparently little relation to pancreatic activity. This, however, I did not try, but turned my attention to amylase, as being the ferment most readily estimated, and not interfered with by the presence of other substances in the blood or urine. Wohlgemuth's method was tried at once and found to be most accurate and reliable. At first the original method was used, with concentrated solutions and a digestion period of twenty-four years. This was soon given up in favour of the most recent modification of the method, which was alone used for the investigations detailed below. I therefore describe this method alone.

The Method.

The substratum used consisted in a 1 per 1,000 solution of ' soluble starch ', the starch being Kahlbaum's special ' Lösliche Stärke '. The exact amount of this (0·5 gramme) was weighed out accurately, and distilled water added. The suspension was heated to boiling and kept boiling for eight to ten minutes with continuous stirring, by which time the fluid had become perfectly clear.

The solution was then allowed to cool, made up to 500 c.c. with distilled water, and transferred to a well-stoppered bottle, a layer of toluol being poured on to prevent entrance of organisms.

The bottle was kept immersed in a bucket of ice-cold water, and could be

kept in this way for a long time without any change; for safety, however, a fresh solution was prepared weekly.

When a urine was to be examined, the first specimen passed in the morning was taken.

This was pipetted into a series of test-tubes, in decreasing quantities, thus :

Tubes	1	2	3	4	5	6	7	8	9	10	11	12
Urine	0·5	0·4	0·3	0·25	0·2	0·15	0·1	0·07	0·05	0·04	0·03	0·02 c.c.

Into each tube 2 c.c. of the starch solution were then rapidly pipetted; the tubes were inverted to ensure mixing, and at once transferred to a beaker of water at 40° C., which, after bringing to approximately 38° C., was placed in an incubator at this temperature.

This was done because an air incubator raises the fluid in the tubes only slowly to its own temperature, so that this is better done by a water-bath which is adjusted to the right temperature and quickly transferred to the air incubator. This is important when working with a short digestive period, as here.

At the end of thirty minutes the tubes were removed from the bath and plunged into cold water to arrest digestion. A few drops of N/50 iodine solution being now added to each tube a beautiful gradation of colour is produced. In the tubes where starch is still undigested the colour is deep blue, where digestion is complete this is yellow, and in the intermediate ones violet and red, this gradation, blue—violet—red—yellow, corresponding to the change from starch to sugar by way of erythrodextrin and achroodextrin.

The tubes which show no blue colour at all are those in which no starch remains, and the lowest of these next to the first purple one is taken as the limit ('Limes')—that is to say, it contains just enough amylolytic ferment to change 2 c.c. of 1/1,000 starch solution.

Reduction to units is done as follows :

x = number of c.c. of urine required to digest 2 c.c. of starch solution (1 : 1,000) in 30 minutes at 38° C.

D 38°, 30″ = number of amylolytic units per c.c. of urine, determined under these conditions.

$$D\,38°, 30'' = \frac{2}{x},$$

e. g. supposing the last tube in the series which contains no blue tint to be No. 6, then

$$x = 0·15 \text{ c.c.},$$

$$D\,38°, 30'' = \frac{2}{0·15} = 13·3 \text{ units.}$$

Corbett (18) used a similar method for determination of amylase in urine. This differed in the particular that the amount of fluid in the tubes was made

constant by making up to 1 c.c. with $\frac{N}{10}$ NaCl solution in each case before adding the 2 c.c. of starch solution. The concentration of starch was, therefore, exactly the same in each tube, the total fluid being always 3 c.c., and this concentration being in general less than in my experiments, the rate of reaction would be less, and the amylase value obtained by Corbett (which is the 'd' of Wohlgemuth) is therefore higher. Theoretically it may be shown that the values of d between certain limits would be rather less than double the corresponding values of D obtained by my method.

The addition of a variable quantity of $\frac{N}{10}$ NaCl, besides being, as it appears to me, unnecessary and involving a separate series of pipettings in every determination made, introduces an element into the reaction which may or may not interfere with its rate. My method was used after trials on the grounds chiefly of greater simplicity, an important factor when a large number of determinations are being made.

As will be seen below, also, the method I used for determination of amylase value of blood-serum was in every way identical with that used for urine, so that the blood and urine values can be correlated in any one case.

In the case of blood-serum, this is obtained by puncture of the antecubital vein with a cannula, the blood being then centrifuged and the serum decanted off. The process of examination is the same as for the urine, the amounts of serum added to the tubes of the series being for convenience :

Tubes	1	2	3	4	5	6	7	8	9	10	11	12
Blood	0·5	0·4	0·35	0·3	0·25	0·2	0·15	0·12	0·1	0·07	0·05	0·04 c.c.

Exactly the same procedure is followed as for the urine, and the value of D per c.c. of serum is calculated as before.

Corbett only made a few determinations of amylase content in blood. For these he used small quantities of serum and diluted five times with saline solution, placing this in small tanks with increasing quantities of starch solution. The value of d has here a different significance to d (urine), since a different method of dilution is used.

I can see no advantage in this method, which seems arbitrary. There is no necessity to dilute the serum, since sufficient can easily be obtained for the determination, and sufficient accuracy cannot be attained without a fairly large volume of serum. I usually obtained a small test-tube full of blood without inconvenience to the patient. In my method, which has also the advantage of greater simplicity, exactly the same procedure is used for serum and urine, and the values of D have the same significance and are therefore comparable.

There is no advantage in using plasma, which Corbett found to give different figures to serum (as might be expected). Here again, theoretically d should be considerably larger than D owing to different dilution—the results both for urine and serum bear this out.

By means of the method detailed, every serum and urine examined has been found to contain amylolytic ferment, and it is clear that amylase is a normal constituent of the blood and urine. This phenomenon is not difficult of explanation. In the case of the stomach the secreting glands are discrete, and the products secreted by the gastric cells have two routes open to them, the most used being the outlet into the lumen of the stomach, where the pro-ferment is activated, and the other being the outlet into the blood-stream, which is used always to some extent, but especially when the stomach is inactive, as is indicated by the pepsinogen content of the urine.

In the case of the pancreas the same is true, though here the secreting cells are assembled to form a gland.

Besides the well-known 'internal secretion' which the pancreas gives up to the blood-stream, part of its ordinary secretion also finds its way into the blood.

Nervous or chemical stimuli cause the pancreas, when food is taken, to produce a copious secretion, which lasts for about half an hour, and then ceases or declines to a continuous level, depending upon the emptying of the stomach. In this way a wave-like secretion is achieved, but in the periods when there is comparative rest from secretion, the products of the gland are probably piled up in the cells and absorbed into the blood-stream to a greater extent than normally. This latter process is of course accentuated by any obstruction to the outflow of the secretions into the intestine, and just as absorption of bile into the blood follows any obstruction of the bile ducts, so an increased absorption of pancreatic ferments into the blood is bound to occur when for any reason their outflow into the duodenum is obstructed.

Icterus has only one significance and origin : the bile comes from the liver only. The pancreatic products in the blood have not such a limited origin, and at this point it may be well to discuss their mode of entrance into the blood.

It has long been known that there is an amylolytic ferment present in the cells of the liver, but this must be so small in amount as to be negligible. In support of this we find that all the cases of simple jaundice, due to obstruction of the bile ducts alone, fail to show any increase in diastatic content of the blood.

An amylolytic ferment is of course secreted by the salivary glands, and some fraction of this may find its way into the circulation.

This amount cannot conceivably be in any way considerable as compared with that derived from the pancreas, but even if it were, in none of the cases I examined was there any evidence of abnormality of the salivary glands, so that any variations from normal in the amylase content of the blood and urine may safely be attributed to the ferment derived from the pancreas. For all practical purposes then we may consider the diastase in the blood to be pancreatic in origin.

In the case of bile salts it has long been known that they are reabsorbed

from the intestine, performing a circle; this may also happen with amylase along with other ferments, but if so I am inclined to put the amount down as very small, as the evidence will show. Wohlgemuth, as mentioned above, found that occlusion of the pancreatic duct in dogs by ligature or inflammation was followed by increase in the diastase of the urine. This operation precluded the outflow of pancreatic secretion to the duodenum, and therefore no theory of reabsorption could explain the increase, for even supposing it to have been excreted by some means into the intestine and reabsorbed, the amount so excreted, and therefore the amount absorbed, would be less and not more than in a normal case.

Neumann, however, maintains that the amylase comes from the intestinal canal, and quotes a peculiar experiment in favour of his theory. By puncture of the thoracic duct of a dog, he obtained just enough chyle to demonstrate that amylase was present, and he demonstrated the ferment in the serum of the same dog, though no quantitative comparison could be made. He assumes from this that amylase finds its way into the blood by absorption from the intestinal tract by means of the chyle duct. As I shall show later, however, I have succeeded in demonstrating amylase in every fluid of the body I have examined, including the cerebro-spinal fluid. We should therefore expect to find it in the chyle also, and Neumann's reasoning falls to the ground. The suggestion that the ferment is elaborated in the blood itself I consider is not worth discussing.

Normal Amylase Content of Blood-serum and Urine.

The amount present in the serum of normal individuals I have found to be practically constant, viz. $D = 6.6$ to 8 units. These I consider the normal limits, and no normal case was examined which gave values outside these limits.

This constancy of the amylase level in the serum of normal individuals is an important fact, and I think that the results which follow justify me in considering any value of D over 8 units in the serum as pathological. In the urine of normal cases a value from 10 to 13.3 units per cm. has been found as the average, though as might be expected the urine shows more variation than serum. I have examined always the first specimen of urine passed in a morning before breaking fast, as I consider this likely to be the most constant and least affected by other factors.

The relation of the amounts 8 units in the blood per c.c. and 13.3 in the urine per c.c. is very interesting in the theory of renal action. The following table shows the values of D in cases in which there was no reason to suspect any abnormality in the digestive or renal systems:

		Blood.	Urine.
A. G.	Normal	8	8
A.	Normal	8	—
A. Q.	Tabes Dorsalis	6.6	13.3
J. B.	Peripheral Neuritis	8	13.3
A. B.	Caries of Spine	8	10
P. S.	Normal	8	13.3
C. W.	Sarcoma	8	10

Physiological Variation.

The blood has been taken at different times during the day, and I have found no reason to suspect any variation in the amylase level of the serum. It appears that there must be a normal level in the blood as 6·6 to 8 units, and that any excess over this is at once excreted by the kidneys. Of the urine many investigations were made, e. g.:

A. Q.   Tabes Dorsalis.   Blood, D = 6·6 units.

Urine.

Time.	D.
5 a.m.	13·2
8 a.m.	20
11 a.m.	13·3
2 p.m.	13·3
8 p.m.	5

A. B.   Caries of Spine.   Blood, D = 8 units.

Urine.

Time.	D.
5 a.m.	10
8 a.m.	20
11 a.m.	13·3
2 p.m.	10
5 p.m.	2·5
8 p.m.	1

E. M.   Chlorosis.   Blood, D = 8 units.

Urine.

Time.	D.
5 a.m.	13·3
8 a.m.	13·3
11 a.m.	13·3
2 p.m.	13·3
5 p.m.	13·3
8 p.m.	8

S.   Normal, with concentrated urine.   Blood, D = 8 units.

Urine.

Time.	D.
5 a.m.	40
11 a.m.	50
2 p.m.	35
5 p.m.	50
9 p.m.	66
12 (midnight)	35

In this case the chief meal came at 5 p.m., in all the others at 12 noon.

S.   Diabetes Mellitus (with impaired renal efficiency).   Blood, D = 8 units.

Urine.

Time.	D.
5 a.m.	2·5
8 a.m.	4
11 a.m.	1
2 p.m.	4
5 p.m.	2·5
8 p.m.	2·5

L. B.   Diabetes Mellitus.   Blood, D = 8 units.

Urine.

Time.	D.
5 a.m.	8
8 a.m.	6·6
11 a.m.	4
2 p.m.	5
5 p.m.	4

A. W.   Carcinoma of stomach involving head of pancreas.
Blood, D = 13·3 units.

Urine.

Time.	D.
5 a.m.	66
8 a.m.	100
2 p.m.	80
8 p.m.	66

It appears from these cases that the concentration of amylase in the urine is at a maximum just after breakfast (8 a.m.), and then decreases gradually, with a secondary rise perhaps after dinner (as seems to be indicated in the cases S. and L. B.), until in the evening it may reach a very low level.
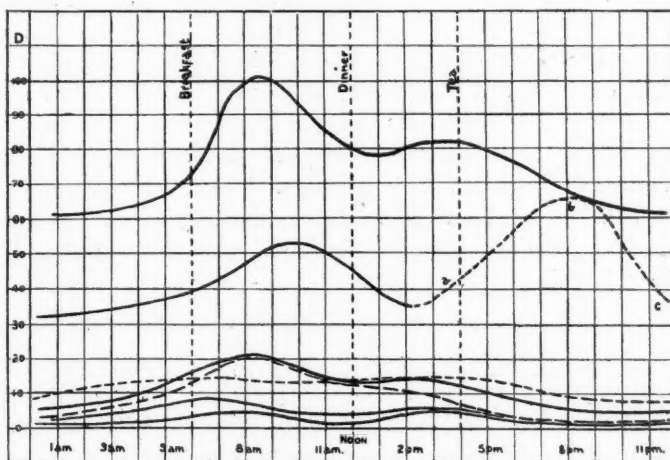
FIG. 1.   Graphic representation of the changes in D (units) in the urine of the cases described.

From the above diagram (Fig. 1) some correspondence between the curves indicating the amylase level in the urine, and what we should expect to be the curve of pancreatic activity, can be readily seen.   The second maximum reached at 9 p.m. in one of the curves (*a b c*) is connected with the fact that in this particular case the principal meal of the day was taken at 5 p. m., with lunch at noon.   Though these variations in D might of course be accounted for merely by variations in the concentration of the urine, their uniformity seems to indicate some relation between the value of D and the digestive processes.

Influence of Sex.

I have found no difference in the value of D in the urine or blood between males and females, and I see no reason why such should exist, though this has been found by some observers.

Influence of Concentration of the Urine.

Several series of experiments were carried out with a view to testing the influence of the concentration of the urine on the value of D per c.c. In the first place, I noticed in several cases in which I had occasion to test the urine at intervals of a few days, that the value of D seemed to vary inversely with the total volume of urine passed in the day on which it was tested.

e.g. J. B.   1st urine (Dec. 18), D = 20, Volume =   795 c.c.
        „   (Dec. 24), D = 8,   „   = 2,187 c.c.
      P.   1st urine (Dec. 11), D = 5,   „   = 7,838 c.c.
        „   (Dec. 16), D = 10,   „   = 3,578 c.c.

From these and other figures I was led to the conclusion that although the value of D varies from day to day with the concentration or amount of urine passed, the total amount of ferment excreted in the urine per diem remains more or less constant, and independent of diuresis or other factors. To test this point further I selected four cases, collected the urine passed in the twenty-four hours on three successive days in each case, and determined the amylase content of the mixed day's specimen. The product of this value and the volume of urine passed gave the total amount of amylase passed on each day. On the second day (after the first specimen had been passed) artificial diuresis was produced by feeding the patient with barley-water.

					1st day.	2nd day.	3rd day.
G. S.	(First morning specimen	.	.	D =	10	10	10)
	24 hours' urine .	.	.	D =	20	16·6	13·3
	Volume of urine	.	.	c.c.	965	1,335	1,704
	Total Amylase in day	.	.		19,300 units	22,161	22,663
J. G. A.	(First morning urine	.	.	D =	8	8	8)
	24 hours' urine .	.	.	D =	8	4	6·6
	Volume of urine	.	.	c.c.	1,306	2,158	1,818
	Total Amylase in day	.	.		10,448	8,632	11,990
P. S.	(First morning urine	.	.	D =	13·3	13·3	13·3)
	24 hours' urine .	.	.	D =	25	13·3	20
	Volume of urine	.	.	c.c.	950	2,110	1,200
	Total Amylase in day	.	.		23,750	26,063	24,000
A. S.	(First morning urine	.	.	D =	8	8	8)
	24 hours' urine .	.	.	D =	8	6·6	8
	Volume of urine	.	.	c.c.	1,021	1.250	1,021
	Total Amylase in day	.	.		8,168	8,250	8,168

It will be seen from these results that the value of D for the twenty-four hours' specimen varied more or less inversely with the amount of urine passed in

the day, so that the total amylase excreted per diem remained approximately constant. In this case the first morning urine gave a constant value for D, the reason for this being of course that diuresis was produced artificially, and the barley-water feeding only began after this specimen had been passed.

Where the urinary volume varies naturally, however, as in the two cases quoted previously, D for the first morning urine varies more or less inversely with this volume. For this reason in all my cases where possible I note the volume of urine for the day as a check on the value of D obtained, and to obtain an approximation to the daily amylase excretion I multiply D by this volume in c.c., calling this product M, e.g.:

		D (1st urine).	Vol. in day.	M.
J. B.	Dec. 18	20	795 c.c.	15,904
	Dec. 24	8	2,187 c.c.	17,494
P. (Diabetes)	Dec. 11	5	7,838 c.c.	39,192
	Dec. 16	10	3,578 c.c.	35,784
R. S.	Dec. 27	40	455 c.c.	18,200
	Jan. 7	10	1,420 c.c.	14,200

It is obvious from the above table that the value of D for the urine, if taken by itself, may be misleading owing to an abnormal concentration; in such cases the value of M serves as a useful check.

The average value for M in normal cases lies between 10,000 and 15,000, but one is not surprised to find considerable variation in this excretion coefficient in different persons. In the same way that two individuals may pass extremely different amounts of nitrogenous bodies, for example, in the urine, and neither be pathological, so I find it to be with amylase. This disparity, however, is not present in the blood to any extent, for, as I have shown above, the normal cases show a remarkable constancy in amylase level in the serum. For this reason, as a check on the urinary results, the amylolytic content of the blood has been estimated in every case of the series.

The Amylase Value as a Test of Pancreatic Efficiency.

Proceeding on the line of reasoning given above, I have attempted to estimate the efficiency of the pancreas with some degree of success. In a few cases the amount of the ferment in the faeces was estimated as well as the blood and urinary contents, e.g.:

	Blood. D per c.c.	Urine. D per c.c.	Faeces. D per grm.
S. (Normal)	8	13·3	38
P. (Diabetes)	—	4	21·3
A. J. (Diabetes)	8	10	5

I may note at this point two experiments on the effect of diet or fasting on the diastase excretion in the urine and faeces. In the *first*, A. J., a case of

diabetes mellitus who was at the time passing about 1,000 grains of sugar per diem, estimations were done on four successive days, on the second of which the patient fasted. The result of the fasting would of course not appear in the faeces until the following day :

A. J. (Diabetes).	Urine.				Faeces.
	D per c.c.	Vol. in day.	M.	Sugar. grm.	D per grm.
Jan. 13 . . .	8	2,780	22,265	1,960	—
Jan. 14 (Fast day) .	8	2,497	19,993	1,056	5
Jan. 15 . . .	5	2,780	13,916	1,078	5
Jan. 16 . . .	10	2,272	22,720	—	5

In this case fasting produced no effect on the amylase of the faeces, but apparently produced a temporary diminution of amylase excretion in the urine.

In the *second* case, P., also a case of diabetes, estimations were again done on four successive days, and on the second day a starch-free diet was given. Here I found, as might be expected, a large increase of amylase in the faeces (since this component of the pancreatic secretion, poured into the intestine along with the other components, which were required by the proteins and fats, had little or nothing to act upon). The urine on the other hand showed no change, which, I think, is another point of evidence against the intestinal absorption theory of the origin or urinary amylase.

P. (Diabetes).	Urine.				Faeces.
	D per c.c.	Vol. in day.	M.	Sugar. grm.	D per grm.
Jan. 13 . . .	4	96	10,905	1,920	—
Jan. 14 (Starch-free diet)	4	104	11,814	2,080	21·3
Jan. 15 . . .	4	112	12,723	2,240	750
Jan. 16 . . .	3	136	11,600	2,720	434

This faecal examination was not proceeded with for several reasons ; not only is it evidently variable from patient to patient, and affected by factors such as diet, but as a test of the pancreatic function it can only be of value where for some reason both pancreatic ducts are occluded near the ampulla of Vater. If any occlusion occurs at some distance along the duct, the flow of pancreatic juice into the duodenum, though diminished, is still present from the part of the pancreas nearest the duodenum, and therefore reliance on this test or on Gross's trypsin estimation in the faeces must lead to error.

In the case of amylase in blood and urine it is quite different. When occlusion of the duct takes place in the region of the ampulla of Vater, the gland becomes turgid with its own secretion, and this being taken up by the blood is indicated by a raised amylolytic value in the serum, and as a matter of course in the urine. When the block is more distal (i. e. farther from the duodenum), the part of the gland distal to the occlusion becomes distended and absorption of the products occurs, though to a less extent than before. In this way disease which is affecting only a portion of the gland and preventing its outflow of secretion may be detected by the blood test, though plenty of ferment may be present in

the faeces. Therefore the estimation of amylase in the blood, and to a lesser degree in the urine, too, has been used in my cases to detect disease of the gland. The same absorption of gland products into the blood-stream we might expect to occur in cases of passive congestion of the gland, and this I find to be shown in my cases of heart and liver diseases.

The pathological processes which may prevent free outflow of gland products, in addition to passive congestion, are: Stone in the duct or ampulla, inflammatory stenosis of duct or ampulla, tumour of head of pancreas pressing on duct, tumour of surrounding area pressing on duct, inflammation of the gland in any part, cyst formation, atrophy of the gland. I propose now to review the results I have obtained in cases of pancreatic disease, following the order of classification in the table.

Acute Pancreatitis.

I had one case, A. A., a woman aged 52, who was sent into hospital as a case of gallstones with the following history. Three days before admission she had been taken suddenly with pain in the epigastrium, which was continuous, and accompanied by frequent biliary vomiting. The temperature was then $100 \cdot 8°$. There was constipation, but no jaundice, and vomiting ceased after the first day. She had no history of any previous attack, nor any previous illness.

On admission the temperature was normal, there was some tenderness over the gall-bladder, and some distension of the abdomen, but no rigidity. The surgeon under whose care she was thought she might be a case of acute pancreatitis and did not operate. I examined the urine on the night of admission and found a very high amylase value, viz. $D = 100$ units—some eight times the normal value. This could not be accounted for by the concentration, which was fairly normal. On the following day the blood-serum was examined and showed a very large increase in amylase content, $D = 20$ units, the normal being, as I have shown above, about $6 \cdot 6$ to 8. The urine contained no albumin, so that the kidneys were apparently functioning normally.

These results gave a definite indication of an acute condition of the pancreas, and I followed up the case by further determinations of the urinary amylase level every few days. The subsequent history was as follows: The patient had no symptoms for a fortnight after admission, save tenderness and a small rise of temperature on the seventh and eighth days of illness, which subsided. During this period I found that the value of D in the urine rapidly declined to a value 20 on the eighth day, at which it then remained constant.

On the eighteenth day there was another acute exacerbation with severe vomiting, absolute constipation, and epigastric pain; the temperature rose to $101 \cdot 4°$, pulse 120. A medical opinion obtained about this time was in favour of a diagnosis of gallstones. I found that with this fresh exacerbation the value of D in the urine again rose to 100, and reached a maximum of 110 on the

twenty-fourth day ; the temperature in the meantime remained about 100·6°. On the twenty-fifth day the patient's condition again began to improve ; vomiting ceased, pulse fell to 92, and temperature remained about 100°, falling to normal on the thirtieth day. Vomiting then again set in, during which the patient brought up a considerable quantity of blood, and death occurred on the thirty-second day of illness.
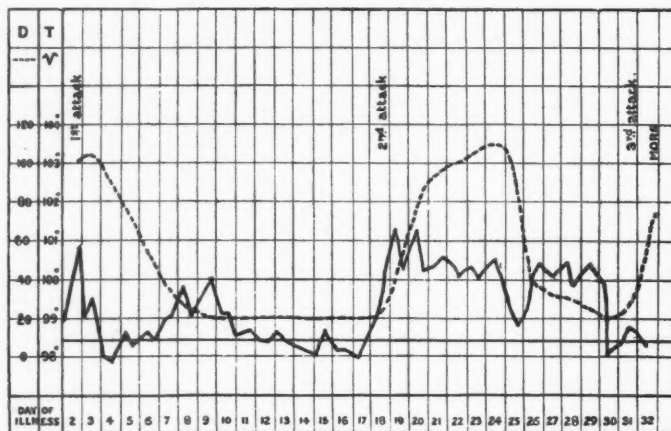
FIG. 2. Case A. A.   Variations in amylase in urine (units).   Dotted line = D units.
Continuous line = temperature.

A post-mortem examination was made, and reported as follows : 'On opening the abdomen a dark coffee-coloured fluid was found free in the peritoneal cavity, especially in the lesser sac, which was full.   There was some adhesion of the intestines together in the upper part of the abdomen.   There were a few patches of fat necrosis in the mesenteric fat.   The pancreas was almost destroyed, and the remnants were covered by the dark fluid, and showed haemorrhages into the gland substance.   The liver showed no signs of cirrhotic change ; the gall-bladder was perfectly normal, and there was no stone in it or in the ducts. The rest of the body showed nothing of interest.'

I have reported this case in detail, not only because I think it is a striking example of the value of the amylase test in the diagnosis of pancreatic disease, but also because it has some bearings on the theory of antiferments, which will be discussed presently.

This case is perhaps not a usual one, in that a number of acute attacks were survived before the end came.   Each of these attacks was, however, typical, and in each case, immediately the patient developed acute abdominal symptoms, the amylase content of the blood and urine per c.c. was found to be largely increased, but subsided again in the intervals.   This is of course due to the inflammatory process obstructing the outflow of secretion and increasing its absorption into the blood-stream.

Accompanying such inflammation in the pancreas is usually a considerable effusion of blood, which serves to make the obstruction more complete, and the

process being so acute, the amylolytic content in the blood is increased tremendously. Such a case may develop conceivably in three ways, if death does not occur. The inflammation may subside, and beyond a little fibrosis no change persists in the gland; or it may lead to cyst formation, as in one of my cases of pancreatic cyst, which had arisen from a traumatic pancreatitis; the third and most unusual method, if the patient survives, is for cirrhotic change to occur, which might practically replace the gland tissue.

Of this latter condition no example has been seen by me, but it is conceivable that in such a case the ferments might be practically absent from the intestinal canal, and from the blood as well. Such cases must be extremely rare, and in none of my cases have I found a markedly subnormal amylase value in the blood.

As I consider that the findings in this case of acute pancreatitis have a bearing on the question of the existence of an antiferment, I propose at this point to note a few experiments which I made to determine the nature of the amylolytic ferment and its action.

Nature and Action of Amylase in Blood and Urine.

Effect of heat and ferment. Blood-serum (from a case of nephritis) was heated at various temperatures with a view to finding at what temperature the ferment activity is destroyed.

Unheated	D = 13·3 units
Heated at 60° for 1 hour	D = 10 „
Heated at 63° for 1 hour	D = 10 „

The serum became semi-coagulated at 64° and could not be pipetted, so that the temperature necessary to destroy its amylolytic activity could not be determined.

Urine (from a case of pancreatic cancer) was then treated similarly.

Unheated	D = 66 units.
Heated at 60° for $\frac{3}{4}$ hour	D = 66 „
Heated at 66° for $\frac{3}{4}$ hour	D = 2 „

The critical temperature therefore lies between 60° and 66° C.

Mode of action. This temperature suggested the possibility of the ferment acting through the medium of a complement which was destroyed at a lower temperature than the ferment itself. The following experiment was carried out with a view to testing this point: Guinea-pig serum was diluted 1 : 10 and the amylolytic value of this fluid determined, and found to be D = 25 : i.e. 0·08 c.c. was just sufficient to digest 2 c.c. of the starch solution.

A urine with a high diastase content was then heated at 66° for an hour to destroy its activity; 0·05 c.c. of guinea-pig serum (diluted 1 : 10) was added to each of a series of tubes containing increasing amounts of the heated urine, along with 2 c.c. of starch solution, and incubated for half an hour.

s 2

Urine unheated   .   .   .   . $D = 66$
Urine heated at 66° for $\frac{3}{4}$ hour .   .   .   .   . $D = 2$
Guinea-pig serum 0·05 c.c. control   .   .   .   . Not digested
Urine heated at 60°, with 0·05 c.c. guinea-pig serum added, still
showed a value $D = 2$.

Hence there is no evidence that urine heated to 66° to destroy its amylolytic activity can be reactivated by the complement present in guinea-pig serum.   This test I found impossible in the blood, since semi-coagulation occurs at this temperature.

Formation of antibodies.   It was the opinion of Wohlgemuth that the amount of diastatic activity gradually fell to the normal value in the blood, owing to the formation or increase of an antibody somewhat akin to the increase of antitrypsin in cases of cancer demonstrated by Brieger and Trebing (16).   From a survey of my cases, especially the case of acute pancreatitis which recurred, and also the case of pancreatic cyst following an injury, it seems much more likely that the chief factor in reducing the amylase to normal level is the kidneys.

In the case described above, a glance at Fig. 2 shows that the amylase level, in the urine at least, follows a curve practically parallel with the temperature graph.   Each successive rise of amylase level due to a fresh attack was of the same height as, or higher than, the one which preceded, and receded as slowly to a low level.   Now if the reduction were due to an antiferment, it is to be expected, as in other phenomena of immunity, that in a series of rises in the amount of antigen introduced (in this case amylase) the antibody would increase to such an extent that the later rises would not be as great as the preceding, or at any rate the fall to normal would be accomplished in a shorter period.   Moreover, the low level, in the presence of increased amount of antibody, might reasonably be expected to be at least the average of health, or lower —which was not so in our case.   Besides this, amylase up to 8 units per c.c. of serum is a normal constituent of the blood, and any substance which is a normal constituent of the blood is not likely to cause formation of an antibody to any extent by its increase.   It is more probable that the subsequent fall from a maximum following a sudden pancreatic obstruction is explicable (if not by removal of the obstruction) by the excretory function of the kidneys, which tends to restore the normal level in the blood or to bring it down to a certain ratio of equilibrium with the urine.

In cases of permanent or more gradual obstruction I find in my cases that a higher level than normal is maintained in the blood, whilst the urine level is increased to a still greater extent, indicating that the kidneys are all the while excreting more ferment in an effort to keep down the blood level, so that a balance is struck between the two.   In one case of pancreatic cyst, to be described later, a large cyst was found containing a highly concentrated solution of the ferments; this had a traumatic origin and had been in existence or

process of formation for seven months. Nevertheless, in this case, I found an amylase value in the blood five times the normal, which was to be accounted for by the obstruction to outflow and back pressure which was occurring, with possibly some absorption of the ferment from the cyst into the blood-stream. Such a large increase persisting for over six months practically disposes of the possibility of antiferment production.

In addition, I may mention here that I have allowed serum and urine to stand for several days, or even a week, without any diminution in the amount of ferment.

Carcinoma of the Pancreas.

These investigations were carried out in a Cancer Research Laboratory, and their prime aim was to determine the possibility of the diagnosis of tumours of the pancreas. On theoretical grounds the method promised a reasonable chance of success, and this is more than borne out in practice.

The most frequent tumours of the pancreas are cancerous, and these are usually located in the head and neck of the gland. A small new growth in this region can easily cause slight obstruction to free outflow of gland products from some part of the gland, even if only of a small fraction. This means that D of the blood-serum is increased. Naturally, however, the retention is never the acute phenomenon here that it is in inflammatory obstruction; the rise of D in the serum is never so high or so sudden as in acute obstruction. In practically all my cases of cancer of the gland I have found a definite and persisting increase of D of the blood-serum, and consequently of the urine. In several cases this finding enabled a diagnosis to be made, where a certain diagnosis could not be arrived at clinically.

In the case of a slight increase in the blood, to say 10 units, the urine also shows a slight increase, but if the urine is very dilute this may escape notice. The blood examination is therefore all-important, and should be done at least once in every case, the urine being examined at the same time. Afterwards, provided there is no kidney disease, the urine alone need be examined to watch the progress of the case.

I propose now to review my cases of carcinoma affecting the pancreas.

J. B. (male) was admitted to hospital with jaundice and ascites, and was thought to be a case of cirrhosis of the liver, though the possibility of malignant disease was suggested. I examined the blood, and found a value $D = 16\cdot6$, considerably above normal. The urine, very dark and bile-stained, containing no albumin or sugar, gave $D = 28\cdot5$ and $M = 32,376$, both being more than double the normal. These figures taken together indicated definite involvement of the pancreas, if not by severe passive congestion, then by growth. In this particular case, beyond the presence of ascites, there were no other indications of portal congestion to any extent; the values were, moreover, a good deal higher than I have found in any of my cases of cirrhosis. There was, therefore, definite evidence of something obstructing both the common bile duct and the pancreatic duct, and on the strength of this carcinoma of the head of the pancreas was

diagnosed. The patient was tapped twice, and the ascitic fluid, which was yellow and clear, had an amylase value $D = 4$ units per c.c. at the first tapping. He then became more deeply jaundiced and was tapped again shortly before death, the fluid this time giving $D = 8$. The post-mortem revealed a large carcinoma of the head of the pancreas blocking the pancreatic and bile ducts, and invading the pylorus, with secondaries in the liver.

A. W. (female) was a case of carcinoma of the stomach at a very advanced stage. The cardiac end seemed to be chiefly involved, and the growth in this region, which was shown by X-rays, was causing some obstruction at the cardiac orifice. The urine was found to contain sugar (but no albumin), which led one to suspect that the pancreas was involved by secondary growths. The blood was found to give an amylase value $D = 13 \cdot 3$, and the urine gave $D = 66$ and $M = 37,480$; all these were considerably above normal. The patient went home in a moribund condition and no post-mortem was obtainable, but I think that the conjunction of an advanced carcinoma of the stomach with glycosuria is sufficient to justify the inclusion of this case among the cases of malignant pancreas.

B. (male) was a case which showed general symptoms of malignant disease, and was thought to be a case of carcinoma of the stomach. There was a hard mass palpable in the region of the pylorus and head of the pancreas, which was also shown by X-rays. The test meal gave a free acidity of 45, so that involvement of the stomach seemed unlikely. I examined the blood and found $D = 13 \cdot 3$, whilst in the urine $D = 13 \cdot 3$ and $M = 13,600$: there was thus a distinct increase in the blood, though the urine was fairly normal. The patient went out of hospital and was lost sight of.

C. D. (male) was admitted to hospital with jaundice of gradual onset, and progressive loss of weight and cachexia. Clinically there was never a doubt about the diagnosis, though no mass could be palpated. An X-ray examination revealed a mass in the region of the head of the pancreas. The urine contained sugar and a trace of albumin; there was no ascites. The blood gave a value $D = 13 \cdot 3$. Several determinations were done on the urine.

6. i. 14.	.	.	.	$D =$	40	.	.	.	$M =$ 45,440
10. i. 14.	.	.	.	$D =$	100	.	.	.	$M =$ 105,080
15. i. 14.	.	.	.	$D =$	40	.	.	.	$M =$ 45,440

All these figures, of course, show a large increase of amylase absorption. The jaundice and cachexia subsequently became more intense, and the patient went home at his own request in a dying condition. This was a classical case of malignant pancreas with unmistakable symptoms and signs, and the diagnosis was clinched by X-rays.

W. L. (male) was sent into hospital as a case of gallstones for operation. He was deeply jaundiced, but there were no general symptoms of malignant disease, nor was the history of onset conclusive in either direction. I examined the blood and found a very large increase in amylase content, viz. $D = 20$. The urine, which was free from albumin or sugar, gave $D = 50$ and $M = 57,300$, both increased fourfold. As will be seen later, and as might be expected, in no case of simple jaundice from gallstones, or other obstruction of the bile ducts alone, have I found any increase whatever in the value of D. I therefore consider that in a case such as the above, which is clinically doubtful, a determination of D is a useful, simple, and reliable diagnostic test between malignant disease of the pancreas and jaundice arising from these other causes. In the case in question it may be interesting to note that a few days previously I applied the test to a case of intense jaundice—G. W. (male), who was thought to be also a case of gallstones (q. v.). In this case I found normal values, viz. 8 and $13 \cdot 3$. Both cases were operated upon. In W. L. no gallstones were found and the gall-bladder was normal, but the pancreas was hard and carcino-

matous along its whole length, so that nothing beyond cholecystostomy could be done. In G. W. gallstones were found impacted in the common bile duct, and the pancreas was normal. In this instance, reliance upon the amylase test would have saved a fruitless operation.

M. B. was a case of intense jaundice with a history suggestive of gallstones, and sent into hospital with that diagnosis. The blood-serum was tested and gave a normal amylase value; the urine, however, showed a very large increase, viz. $D = 66$ and $M = 37,455$, and contained an enormous quantity of bile. No operation was done, and a post-mortem six weeks later revealed a carcinoma arising in the upper part of the head of the pancreas and involving the lesser sac of the peritoneum and bile ducts. The large values of D and M in the urine in this case were sufficient to indicate pancreatic involvement. The normal value in the blood-serum seems anomalous, but might perhaps be explained by increased permeability of the kidneys, as seemed to be indicated by the enormous amount of bile excretion in this case.

F. J. was a patient who was being treated for pernicious anaemia. The blood film, however, was not conclusive, and thinking there might be a possibility of carcinoma of the pancreas, I examined the blood and found $D = 10$, and in the urine $D = 28.5$ and $M = 63,954$, all of these being considerably above normal. An X-ray was therefore taken, and revealed a mass which appeared to be involving the stomach and possibly the pancreas. The patient was lost sight of.

H. S. was a case with marked glycosuria and very severe cachexia, which led the physician in charge to a diagnosis of carcinoma of the pancreas. The blood was found to give a high value, $D = 16.6$, whilst the value of M in the urine was normal. No further evidence was obtained.

The remaining two cases were both obscure clinically, one having a palpable mass in the epigastrium, and the other suffering from profound cachexia without obvious cause. The possibility of pancreatic carcinoma was suggested, and in each case I found a large increase in amylase content of blood-serum and urine. The cases are included here, though no further evidence was obtained up to the time of writing.

Melanotic Sarcomatosis, involving the Pancreas.

I had one case which showed a slightly raised amylase level in the blood ($D = 10$). The post-mortem showed innumerable tumours all over the body, especially in the heart and endocardium, evidently secondary to a melanotic growth removed from the eye two years previously. The liver was much invaded, and the pancreas was slightly larger than normal, and in its whole length invaded by numerous hard little tumours.

Pancreatic Cyst.

Of this rare condition I was fortunate enough to come across two cases, and found in both a considerable increase in D.

Mrs. G., my first case, was a patient in the Salford Hospital, and was admitted with a tumour in the upper part of the abdomen. It was suggested that this might be a cyst of the pancreas, and I therefore examined the blood and urine, and found $D = 13.3$ and 40 respectively. This indicated some interruption of free outlet of secretion from some part of the gland, which might readily be caused by a cyst, for it is to be expected that in the early stages at least a cyst will cause a progressing obstruction to free outflow of secretion from part of the gland distal to it.

In a very chronic case of cyst formation it is conceivable that the pancreatic products do not go freely into the intestine, neither are they absorbed to any extent into the blood, and such a case might present difficulties of diagnosis by amylolytic estimation or by any chemical means. I have not come across any case of this kind, since both my cases were of fairly recent origin. In the case in question the diagnosis was confirmed by operation, which revealed a cyst arising from the middle of the body of the pancreas.

S. B. (male) was a still more interesting case. He gave the following history : Seven months before admission to hospital he had fallen heavily from his bicycle, driving the handle-bar forcibly into the 'pit of his stomach'. He had suffered from severe pain at the time and this had recurred and persisted ever since to some extent. There was nothing very definite to be felt on palpation, and the surgeon's diagnosis was duodenal ulcer. A specimen of urine was taken before operation (though pancreatic cyst was never suspected in this case), and blood was taken at the operation. In both I found a very large increase in the ferment: for the blood $D = 40$, and for the urine (normal concentration) $D = 80$. On opening the abdomen a fairly large cyst was discovered arising from the pancreas, containing dark blood-stained fluid, in which we found blood, albumin, and a high concentration of pancreatic ferment. The cyst fluid gave a value $D = 2,000$. The enormous increase in the blood was remarkable in a case of six months' duration; probably in addition to back pressure through obstruction to outflow, some absorption was taking place from the large area of cyst-wall in contact with such a concentrated solution of the ferment.

Conditions causing Passive Congestion of the Pancreas.

Venous congestion of the pancreas may arise either from general passive congestion, as in mitral stenosis or bronchitis and emphysema, or from portal congestion due to cirrhosis of the liver.

I examined two cases of the first type, with very obvious generalized venous stasis.

	Blood.	Urine.	
M. E. R. (Female) Mitral stenosis	$D = 13\cdot3$	$D = 66$	$M = 46,860$
W. (Male) Chronic bronchitis and emphysema .	$D = 13\cdot3$	$D = 40$	$M = 127,200$

In both cases I found a considerable increase in amylase values, due to venous stasis in the gland causing increased absorption of its products by the blood. The same was true, though to a less extent, since the congestion was not so severe, in cases of cirrhosis of the liver.

		Blood.	Urine.	
W. J. (Male)		$D = 13\cdot3$	$D = 20$	$M = 17,040$
W. L. (Male)		$D = 10$	$D = 5$	$M = 2,124$
M. B. (Female)		$D = 10$	$D = 10$	$M = 7,384$

In the last two cases there was some albuminuria, indicating some deficiency in the kidneys, which would account for the somewhat low values found in the urine. Ascites was present in the first two cases, and in each case the fluid was examined.

In W. J. 204 oz. of fluid were withdrawn, with a specific gravity 1,015 and albumin 1·8 per cent.; the fluid gave a value $D = 5\cdot7$, or about half that in the blood-serum.

In W. L. 198 oz. were taken away, specific gravity 1,017, albumin 1·8 per cent.; in this case I found $D = 1$, probably because the excess in the serum was much less than in the previous case. The diagnosis was afterwards confirmed by post-mortem.

The above results indicate that before drawing any conclusions with regard to pancreatic disease from a slightly raised value of D in the blood, it is necessary to exclude venous congestion as a cause. If this, however, is present in sufficient degree to raise the value of D appreciably, it will, I believe, always be clinically obvious.

Other Conditions producing some Obstruction of the Pancreatic Duct.

I had three cases in which I found a raised amylase level, which I believe were explained by obstruction to the duct by scar-tissue and adhesions.

E. B. (female) had been operated upon for gallstones six months previously, and the gall-bladder had been removed. She came back to hospital complaining of vague pains in this region, with some vomiting. I examined the blood and found $D = 20$, $M = 19,880$, indicating some obstruction to outflow of secretion. An X-ray examination was made, and showed evidence of some obstruction in the duodenum with adhesions, probably due to scar-tissue following the cholecystectomy.

T. F. (male) was admitted to hospital with a history of slight varying jaundice for eighteen months, and some loss of weight. There had been no gall-stone colic, but there was some tenderness over the gall-bladder. The possibility of malignancy of the pancreas was suggested. The blood gave a value $D = 10$, and urine $D = 20$ and $M = 21,016$. I did not consider this increase sufficient to indicate carcinoma. A laparotomy was performed and the pancreas was found to be normal, but there were extensive adhesions round the duodenum and gall-bladder and ducts, also in the appendicular region. The scar-tissue and adhesions found in these two cases involving the duodenum and ducts would readily account for the slight increase found.

The third case, J. C., was diagnosed as a case of tuberculous peritonitis. The abdomen was felt in its upper part to contain a large hard mass of omentum, so hard as to suggest that it might be carcinomatous. I therefore determined the amylase content of the blood and urine and found D (blood) $= 13·3$, D (urine) $= 100$, and $M = 113,600$, all showing a very large increase, which I thought probably indicated a carcinomatous involvement of the pancreas. A post-mortem, however, showed that all the abdominal viscera were densely matted together and involved in tuberculous peritonitis, the condition being quite sufficient to produce extensive obstruction to the outflow of ferment from the pancreas.

Before passing on to the consideration of diabetes mellitus, I wish to mention in passing, though without laying any emphasis upon it, a case which was brought to my notice through the courtesy of Dr. Leech with the suggested diagnosis of pancreatic infantilism.

This was a girl aged 10, who had obviously had rickets, but suffered from persistent diarrhoea for five or six years, and was small and somewhat backward in development. The blood gave $D = 16·6$, and the urine $D = 50$ and $M = 19,600$. I had no opportunity of testing the faeces. I do not attempt to explain the large increase in D found in this case, associated as it was with continuous diarrhoea and deficient development. The possibility of a congenital anomaly of the pancreas suggests itself. I think the case, however, worth reporting.

Diabetes Mellitus.

Some observers, viz. Wynhausen and Rosenthal, as mentioned in discussing the literature, found a diminished amylase coefficient in the urine of diabetics, which diminution they found to increase with the severity of the disease. They therefore attached significance to this decrease as a sign of prognostic value.

It is of course obvious that with the large increase in volume of urine passed in the day, the concentration of all the constituents of urine (except sugar) diminishes with the amount of urine passed, which in itself is some sort of an index of the severity of the case. I do not, therefore, consider it in any way remarkable that a diminished amylase concentration is found; one might just as well measure, for example, the diminished concentration of urea and attach significance to this.

In the majority of my cases the total amylase excretion per diem, approximated to by the value of M, was found to be either normal, or in some cases increased, and in only one case was this subnormal, though in all cases the value of D was diminished.

Though I cannot claim to have tested many cases, I regard it as a fallacy to place any emphasis on a reduced value of D in the urine as a phenomenon typical of diabetes mellitus; it would be of equal value as a sign of diabetes insipidus, or other condition giving a large quantity of dilute urine.

In cases in which both D and M have been found subnormal in urine, it is most probably an effect of kidney disease, nephritis being very common in diabetes. Some observers have found a decrease in both blood and urine in some cases; it is possible that these were cases of cirrhosis of the pancreas which have developed glycosuria, in which a reduced value of D would be typical. I have not come across any such cases.

With regard to D in the blood, I found normal values in three cases, a slight increase in one case (W. H.), and in one very severe case in which fourteen pints of urine were being passed in the day I found a large increase in D (blood), viz. $D = 28 \cdot 5$, and also a large increase in M (urine). I cannot adequately explain this last case (P.), but possibly the diabetes was secondary to extensive disease of the pancreas which interfered also with its ferment-secreting function.

There was no albuminuria or evidence of kidney disease in any of these cases; diacetic acid was present in all.

| | | Blood. | | Urine. | | |
		D.	D.	Volume. oz.	M.	Sugar. grm.
S.	(Male)	8	2·5	32	2,272	896
L. B.	(Male)	8	8	72	16,358	1,150
A. J.	(Male)	8	10	122	34,648	2,196
W. H.	(Male)	10	10	62	17,608	2,170
P.	(Male)	28·5	5	276	39,192	1,380

Diabetic Coma.

I had two cases of diabetic coma, which ended fatally, and in both cases the determinations were made just before death. In both instances there was a considerable amount of albumin in the urine and an enormous quantity of diacetic acid. The blood gave in one case a high value $D = 13 \cdot 3$; this might be explained by the fact that the kidneys were not excreting properly, as indicated by the albuminuria (or by the general disturbance of metabolism occurring just before death). The urine also showed some increase in value of M.

							Blood.	Urine.	
W. R.	(Male)	.	.	.	.	.	D = 13·3	D = 10	M = 34,080
A. T.	(Male)	.	.	.	.	.	—	D = 20	M = 39,760

Relation between Sugar and Amylase Excretion. I carried out a few experiments to test whether there was any relation between the total sugar excretion and total amylase excretion per diem in diabetics. No obvious relation was found, but I append the results.

				Date.	Vol. of Urine. oz.	Sugar. grm.	D.	M.
W. H.	(Male)	.	.	Dec. 22	62	2,170	10	17,608
				Jan. 10	90	1,800	5	12,780
				Jan. 12	76	1,520	6·6	13,242
				Jan. 13	84	1,680	10	23,856
				Jan. 16	68	1,360	13·3	25,683
				Feb. 8	70	nil	10	19,880
P.	(Male)	.	.	Dec. 11	276	2,000	5	39,192
				Jan. 12	98	1,960	8	22,266
				Jan. 15	112	2,240	4	12,723
				Jan. 16	136	2,720	3	11,600

Nephritis.

Most of my cases of nephritis showed a raised amylase level in the blood and diminished values of both D and M in the urine. In all these cases there was therefore decreased permeability of the kidneys to the ferment, and in no case did I find an increased permeability.

				Blood. D.	D.	Urine. Vol. oz.	M.	Esbach.	Total Albumin excreted. grm.
Acute									
F. C.	.	.	.	10	2	16	909	7	56
Chronic Parenchymatous									
T.	.	.	.	6·6	5	36	5,112	0·25	4·5
D.	.	.	.	16·6	1	56	1,590	1	28
W. W.	.	.	.	13·3	10	55	15,620	0·5	13
J. B.	.	.	.	8	8	77	17,494	4	154
B.	.	.	.	20	2	32	1,818	8	128
J. J.	.	.	.	16·6	13·3	—	—	2	—
E. S.	.	.	.	13·3	3	37	3,152	4	0·74
Chronic Interstitial									
C.	.	.	.	13·3	—	—	—	—	--
C. T. B.	.	.	.	13·3	—	—	—	—	—

The table shows one marked exception, J. B., in which the values of D (blood) and M (urine) were normal; this was tested more than once, thus:

J. B.   Blood D = 8.   Urine D = 20   M = 15,904.
                              D = 8   M = 17,494.

With this exception, which was a case of very long duration, in general the increase in D for the blood varied more or less in proportion to the severity of the disease as gauged by the total albumin excretion. I think then that Wohlgemuth's claims on behalf of the estimation as a test of renal efficiency

seem well grounded. In no single case has amylase been found absent from the urine, although its limits in renal disease have been wide. It can readily be seen from these results why the kidney condition must always be kept in view, and also why the estimation of amylase in urine alone is useless in many cases. It is better always to estimate the amylase in the blood at least once, and in the urine at the same time. Any serious disparity in the ratio D (blood), D (urine), or at any rate D (blood), M (urine) indicates disease of the kidneys, and narrows the range of usefulness of the estimations as a test of pancreatic efficiency.

Diseases of the Liver and Gall-bladder.

In all cases of gallstones I found normal values of D. One of these, G. W. (female), which I referred to in considering carcinoma of the pancreas, was deeply jaundiced, with a long history rather suggestive of malignancy. The tests showed D normal in the blood and urine (8 and 13·3 respectively), and at operation a gallstone was found impacted in the common bile duct. This and other cases led me to regard the test of the utmost value in distinguishing between jaundice arising from gallstones and pancreatic carcinoma. E. T. (female) was a case in which there was clinically no question of the diagnosis of gallstones, and gave D (blood) = 8, and for urine D = 8 and M = 7,043. The other two cases, both of which gave normal values, were diagnosed clinically, and the diagnosis was confirmed by operation.

Other Diseases.

A case of chlorosis showed nothing abnormal. I tested one case of Hodgkin's disease, which was running a high temperature; I found a slight decrease (D = 10) in the blood, and normal values in the urine. This slight increase was probably to be explained by increased metabolism due to the high temperature, since other observers have found increased values in acute fevers. A case of mitral stenosis, which was well compensated at the time, gave normal results.

In R. S. (male), with pleural effusion extending up to the third rib and causing displacement of the heart, and some slight rise of temperature, I found a slight increase, viz. D (blood) = 10. The pleural fluid, which was clear, yellow, and coagulated on standing, gave D = 8. The urine was twice tested and showed a slight increase in M, thus:

27. xii.   D = 40.   (454 c.c.)   M = 18,176.
7. i.   D = 10.   (1,420 c.c.) M = 14,200.

These results were probably explained by venous stasis.

I examined four cases of carcinoma of the stomach.

E. M. (female) was a case in an advanced stage, with coffee-ground vomiting; the blood gave D = 10, and urine was normal. A distinct mass was palpable at the pylorus. It was more than likely that the pancreas or its duct would be to some extent involved, which would explain the slight rise in D.

E. D. (female) had marked obstruction at the pylorus, which could be felt thickened. Here again a moderate increase in D was found, both in blood and urine (D = 10, 28·5). On operation a fairly large carcinoma was found at the pylorus, which was of course pressing upon surrounding structures. Though no secondary growths could be felt, these may have been present in the pancreas, or if not, the mechanical pressure of the tumour might account for the obstruction to escape of secretion, as indicated by our results.

The other two cases showed no increased but rather diminished values of D. I applied the test also to a number of cases with epigastric tumours, many of which remained undiagnosed. I append the results at the end of the table.

Conclusions.

(1) Amylolytic ferment is present in the blood-serum and urine of all healthy individuals, and has also been found in all the body fluids examined.

(2) The level is practically constant in the blood-serum—the level in the urine is subject to diurnal variations due chiefly to the digestive functions.

(3) The ferment is of pancreatic origin and is absorbed directly by the blood.

(4) No proof of the action of antiamylase has been found.

(5) Disease of the kidneys causing any diminished permeability of these organs reduces the amount of ferment in the urine and consequently raises the amount in the blood.

(6) Any disturbance in the ratio D (blood) : D and M (urine) indicates renal insufficiency in all such cases.

(7) Severe passive congestion also raises the amount of amylase in the blood.

(8) With these exceptions any increase of the ferment in the blood-serum denotes pancreatic mischief.

(9) The values have been found raised in all cases of pancreatic disease, the increase depending on the degree of obstruction in any part of the gland or its ducts, and on the acuteness of the condition.

(10) The highest values were found in a case of acute pancreatitis.

(11) The estimation of the amylolytic capacity of the blood-serum and the urine is a most delicate test of the efficiency of the pancreas, and consequently is a most delicate and reliable test for disease of the pancreas.

(12) The use of the simplified modification of Wohlgemuth's method, and the use of an identical technique for serum and urine, are justified by the consistency and regularity of the results obtained.

In conclusion, I wish to record my indebtedness and thanks to Dr. Reynolds for kindly enabling me to undertake this work and for his advice in the matter, and to Dr. W. J. Reid, under whose direction this research was carried out, and for his valuable help and unfailing courtesy and kindness throughout. My thanks are also due to those who have allowed me to make use of their cases for the purposes of these investigations.

TABLE OF RESULTS.

D = Number of diastase units per c.c., as defined above.
V = Volume of urine passed in the day, in c.c.
M = D × V (where D is measured for the first urine passed).

I. *Normal Cases.*

No.			Blood. D.	Urine. D.	D.	M.
1	A. Q.	Tabes Dorsalis .	6·6	13·3	852	11,330
2	A. B.	Peripheral Neuritis	8	10	1,250	11,360
18	J. B.	Peripheral Neuritis	8	13·3	1,136	15,108
19	P. S.	Normal	8	13·3	1,136	15,108
42	A.	Normal	8	—	—	—
50	A. G.	Normal	8	8	1,988	15,904
58	C. W.	Sarcoma	8	10	852	8,520

II. Diseases of the Pancreas.

No.	Diagnosis.	Blood. D.	Urine D.	V.	M.	Sugar.	Albumin.	Diacetic acid.	Cyst Fluid. D.
Acute Pancreatitis									
45. A. A.	Post-mortem	20	110	994	109,340	—	Trace	—	—
Carcinoma									Ascitic Fluid
28. J. B.	Post-mortem	16·6	28·5	1,136	32,376	—	—	--	8
36. C. D.	Clinically and X-ray	13·3	100	1,051	105,080	+	Trace	—	—
52. W. L.	Operation	20	50	1,136	57,300	—	—	—	—
10. A. W.	Clinically	13·3	66	568	37,480	+	—	+	—
24. B.	Clinically	13·3	13·3	1,022	13,597	—	—	—	—
53. M. B.	Post-mortem	8	66	568	37,455	—	—	—	—
39. F. J.	X-ray	10	28·5	2,243	63,954	—	—	—	—
66. H. S.	Clinically	16·6	5	2,272	11,360	+	—	+	—
62. F. F.	Clinically	16·6	40	1,306	52,256	—	—	—	—
22. C. H.	Clinically	13·3	20	1,846	36,920	—	—	—	—
Melanoma									
38. S.	Post-mortem	10	10	767	7,670	—	—	—	—
Cyst									
14. G.	Operation	13·3	40	—	—	—	—	—	—
61. S. B.	Operation	40	80	1,704	136,320	—	—	—	2,000
Passive Congestion									
(i) *General Venous Congestion*									
5. M. E. R.	Mitral stenosis	13·3	66	710	46,860	—	—	—	8
25. W.	Chron. Bronchitis and Emphysema	13·3	40	3,180	127,232	+	Trace	—	—
(ii) *Portal Congestion*									
6. W. J.	Cirrhosis of Liver (Ascites)	13·3	20	852	17,040	—	—	—	5·7
8. W. L.	Cirrhosis of Liver (Ascites)	10	5	625	2,124	—	+	—	1
46. M. B.	Cirrhosis of Liver	10	10	738	7,384	—	+	—	—
Other Conditions obstructing Duct									
40. E. B.	Adhesions following Cholecystectomy (X-ray)	10	20	994	19,880	—	—	—	—
51. T. F.	Adhesions round duodenum and gall-bladder. (Found at operation.)	10	20	1,051	21,016	—	—	—	—
60. J. C.	Tuberculous peritonitis with extensive adhesions. (Post-mortem.)	13·3	100	1,136	113,600	—	—	—	--
Pancreatic Infantilism?									
49. E. M. (Aged 10)		16·6	50	653	19,600	—	—	—	—

III. *Diabetes Mellitus.*

No.		Blood.	Urine.					Dia-cetic acid.	Albu-min.
		D.	D.	V.	M.	Sugar. grm.			
7.	S.	8	2·5	909	2,272	896		+	—
9.	L. B.	8	8	2,045	16,358	1,150		+	—
26.	P.	28	5	7,838	39,192	1,380		+	—
30.	A. J.	8	10	3,465	34,648	2,196		+	—
32.	W. H.	10	10	1,761	17,608	2.170		+	—
Diabetic Coma									
56.	W. R. . . .	13·3	10	3,408	34,080	?		+ +	+
59.	A. T. . . .	—	20	1,988	39,760	?		+ +	+

IV. *Nephritis.*

No.		Blood.				Urine. Albumin.			
		D.	D.	V.	M.	Parts per mille.	Grm. in die.	Sugar.	Blood.
Acute									
4.	F. C. . .	10	2	454	909	7	56	—	+
Chronic Parenchymatous									
20.	T. . .	6·6	5	1,022	5,112	0·25	4·5	—	—
21.	D. . .	16·6	1	1,590	1,590	1	28	—	—
27.	W. W. . .	13·3	10	1,562	15,620	0·5	13·5	—	—
29.	J. B. . .	8	8	2,187	17,494	4	154	—	—
31.	B. . .	20	2	909	1,818	8	128	—	—
34.	J. J. . .	16·6	13·3	—	—	2	—	—	—
48.	E. S. . .	13·3	3	1,051	3,152	4	74	—	—
Chronic Interstitial									
12.	C. . . .	13·3	—	—	—	—	—	—	—
35.	T. C. B. . .	13·3	—	—	—	—	—	—	—

V. *Diseases of the Liver, Gall-bladder, and Stomach.*

No.		Blood.	Urine.			Bile.	Albn.
		D.	D.	V.	M.		
Gallstones							
47.	G. W. (Operation).	8	13·3	1,136	15,008	+ +	—
55.	E. T. . . .	8	8	880	7,043	Trace	—
64.	A. K. (Operation).	6·6	13·3	—	—	+	—
65.	M. K. (Operation).	8	13·3	994	13,220	+	—
Stomach, Carcinoma							
23.	E. M. (Advanced).	10	13·3	1,164	15,485	—	—
15.	W. B. (Pylorus) .	8	6·6	895	5,247	—	—
63.	E. D. (Pylorus) .	10	28·5	895	24,343	—	—
57.	M. (Pylorus) .	5·7	10	—	—	—	—
Cirrhosis of Liver							
—	See Congestion of Pancreas.						

VI. *Other Diseases.*

			Blood.		Urine.			
			D.		D.	V.	M.	Albn.
Blood Diseases								
3.	E. M.	(Chlorosis) . .	8		13·3	937	12,460	—
17.	A. S.	(Hodgkin's) . .	10		10	1,136	11,360	—
Heart, Lungs								
11.	T. A. B.	(Mitral stenosis compensated)	8		10	1,193	11,928	—
33.	R. S.	(Pleural effusion) .	10 Fluid D = 8		10	1,420	14,200	—
Epigastric Tumours (not diagnosed)								
13.	J. A. W. .	. . . .	10		8	568	4,544	—
37.	C. D.	. . . .	8		4	1,448	5,793	—
43.	S. .	. . . .	6·6		4	1,092	4,365	—
58.	C. W.	. . . .	8		10	852	8,520	—

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URTICARIA TUBEROSA OF WILLAN

By J. A. NIXON

Historical Survey.

THE term 'urticaria tuberosa' was first used by Frank (1) in his work *De Curandis Hominum Morbis*, 1792. In his account of the exanthemata he applied the term to a large group which now would include the manifold varieties of angeio-neurotic oedema. His definition of urticaria tuberosa reads thus: 'A definition of this exanthem is, from its inconsistency, difficult. We shall not form a bad idea of the disease if we describe it as an efflorescence, often but not always accompanied by fever, consisting sometimes of macules like nettle-stings, sometimes of tumours surmounted by a vesicle, or even of great protuberances in the skin. It usually begins towards night with intense itching of the skin and a slight fever, or it may break out profusely upon exposure of the skin to cold, itching intolerably. The rash disappears readily but soon breaks out again with scratching, but after a few days it usually subsides without desquamation of the epidermis.' Frank gives a detailed description of a young man, aged 20, affected by this form of urticaria, which seems indistinguishable from any other form of food urticaria attended by gastro-intestinal disturbance and a profuse nettle-rash.

Willan (2), however, in 1808, distinguished this variety of urticaria rather more clearly than Frank from the general group. 'In the urticaria tuberosa', he says, 'many of the wheals increase to a large size, forming hard tuberosities, which seem to extend deeply into the muscular flesh, and occasion a contraction in the sinews, with total inability of motion, and a sensation of pain in the bones. These tumours are usually whitish at their tops: they rise on the arms, thighs, loins, and calf of the leg, and are very hot and painful for several hours. The eruption, in all cases under my observation, took place at night, and before morning it wholly disappeared, leaving the patient weak, languid, and sore, as if he had been bruised, or had undergone much fatigue.'

Cazenave (3), 1827, gives a good account which Rayer follows very closely of a case observed in Biett's clinic. Bateman (4), 1829, gives his description in Willan's words, prefacing them with the remark: 'This species which was named by Dr. Frank.' Rayer (5), 1835, is the next to refer to this variety of urticaria: 'Chronic urticaria, however, is sometimes seen with more serious characters (urticaria tuberosa of Willan). The disease does not then consist in mere slightly prominent elevations, but in true tuberosities of various magnitudes, hard, deep-seated, extending to the subcutaneous cellular tissue, sometimes accompanied by true ecchymoses, by pain in moving the limbs, and a tense very sore state of the skin. These tumours, which are very itchy, appear in the evening or at night, and disappear again entirely before morning, leaving the patient weak, restless,

and weighed down with languor and depression.   They come out more particularly
on the loins and extremities, but they may show themselves over the whole of
the body, cause a general swelling of the face, of the neck, and of the limbs; be
accompanied by dyspnoea, irregularity in the action of the heart and other
symptoms distressing in various degrees which are commonly developed under the
influence of a febrile paroxysm (febris intermittens urticata, Frank).   The eruption
disappears completely with the remission of the fever and appears with its accession.'

    After this time, the variety named by Willan, urticaria tuberosa, seems to
have been lost sight of.   Demarquay (6) in 1842, described the treatment of
several cases of urticaria tuberosa, but this is an article in praise of arsenic
rather than a particularly careful account of the conditions treated.   He quotes
indeed Frank and Bateman, and at greater length Rayer and Cazenave, but his
cases include one of acute circumscribed oedema with hydrarthrosis and a septic
case with enormous painful swelling of the limbs and ulceration of the skin.

    Graves (7), 1843, came nearer to the truth when in his ' Clinical Lectures '
he wrote : ' You will allow that the connexion between arthritis, disease of the
digestive organs and urticaria can no longer be considered as fortuitous.'
Speyer (8) in 1853 published an article entitled ' Urticaria Tuberosa Frankii ' in
which a general description of urticaria is given without attention to the
distinctive features upon which Willan based his classification.   Fouquet (9),
1865, gives the most complete survey of the early references to urticaria tuberosa
that I have been able to find.   Although he credits Frank with having first used
the name, he is inclined to consider the single case which Frank recorded as being
a doubtful instance of the disease.   Fouquet comments on the extreme rarity of the
condition, and the very few examples which had to that time been reported.   He
rejects Fuch's three cases recorded under this title, as well as Biett's case described
by Cazenave, which is, as he says, quoted at length in most books on dermatology,
although, being unique, it cannot properly be regarded as a confirmation or
illustration of this variety of urticaria.   Fouquet suggests that the condition
called by Frank ' urticaria tuberosa ' very soon lost its identity in Bateman's
' erythema nodosum '.   He does not, however, mention that the disease as
described by himself was first completely differentiated by Willan under the title
' urticaria nodosa seu tuberosa ', nor does he seem to appreciate the close similarity
between his own description and Willan's.

    Fouquet regarded the disease as peculiar to the female sex, occurring usually
between the years of puberty and the climacteric, and generally associated in
some way with the uterine functions.   There is, as a rule, no prodromal stage.
An eruption suddenly appears consisting of a few rapidly developing wheals
which change incredibly quickly into hard, sharply defined nodes or knobs of
round, oval or irregular shape, sometimes attaining on the loins to the size of
the hand.   These elevations are white, with occasionally a slight erysipelatous
reddening around.   The eruption is accompanied by a burning pain which
renders movement difficult.   The tuberosities are apt to appear at nights and
disappear by the morning (epinyctides).   The head and face are not affected, the

favourite sites being the lower limbs and loins.   The tuberosities are hard,
freely movable, and do not itch, but cause an intolerable burning or aching pain.
They are deeply seated in the true skin, but Fouquet does not accept the state-
ment of some authors that they involve the subcutaneous cellular tissue.   He
lays special stress on their ephemeral nature ;   there are rarely more than two or
three tuberosities present at one time, they disappear as a rule within twenty-four
hours, and a fresh crop will break out every night.   This tendency to recurrence
may last from a fortnight up to several months, with increasing periods of
freedom, and a diminution in the size of the nodes.   The patients feel weak,
exhausted, and sore, as if their limbs had been beaten.   Fouquet describes five
cases with almost identical symptoms occurring in women of child-bearing age
varying from about 30 to 50.   He admits that the immediate causation is absolutely
unknown, and that the treatment is unsatisfactory.   Cold and exposure to
wind and weather may precipitate an attack, while warmth relieves the pain.
Heating food or drink aggravates the condition.   The preference for the female
sex and some relation to disturbed sexual functions he regards as indisputable.

Morrant Baker (10), 1881, once again made use of the term to describe an
ordinary case of superficial urticaria complicated by Bazin's erythema induratum.

.   .   .   .

A new era, however, commenced with Quincke's masterly description of
acute circumscribed oedema in 1882.   Beyond acknowledging the merits of
Quincke's observations there is small need to recapitulate his conclusions, which
tended to direct attention away from Willan's urticaria tuberosa.   So that since
this period, urticaria tuberosa appears to have been lost sight of.

Although pathogenetically the condition is allied to Quincke's acute
circumscribed oedema, the patients subject to the disease are not diagnosed
as suffering from an affection of the kind described by Quincke.   So much is
this the case, that, after the appearance of acute circumscribed oedema in our
nomenclature, the term urticaria tuberosa vanished.   This would be a matter
of small moment if the condition were still recognized under Quincke's classifica-
tion as an oedema or an urticaria.   In point of fact, however, the cases have
been relegated to the lumber heap of chronic rheumatisms and discouraging
prognoses accordingly given to the sufferers.

Dubreuilh (11), 1892, objected to the name acute circumscribed oedema, and
suggested as an improvement 'urticaire œdémateuse', but he describes a form of
urticaria in which nodules occur without pyrexia or local heat.   The nodules are
very hard, and scarcely red.   Itching is slight or absent, but there is a disagreeable
sense of tension.   He gives an excellent description of this nodular urticaria in the
fingers, where 'if the swelling is not obvious to the eye, it is very clearly perceived
by the patient, who feels his fingers so swollen that it is painful to bend them '.

Collins (12), 1892, temporarily replaced the condition in its right cate-
gory, when in his description of angeio-neurotic oedema he gives as synony-
mous titles 'acute circumscribed oedema, acute idiopathic oedema, periodic
swelling, urticaria tuberosa or giant swelling, acute non-inflammatory oedema,

Australian blight'. He uses the term ' urticaria tuberosa ' as the equivalent of the whole group of angeio-neurotic oedemas, and not in the more restricted sense of Willan. But he makes the important observation : ' this condition has a close relationship to the many oedemas spoken of, and also a family relation with many of the arthropathies as yet not well understood, but known to be directly caused through the agency of the nervous system.' Osler (13), 1909, refers to this type of urticaria very briefly : ' a peri-articular variety has been described.'

Garrod (14), 1907, admits ' that there are good reasons for thinking that such a transient arthritis as that of rheumatic fever has a close kinship with such inflammatory forms of oedema as are met with in the erythemas and urticaria, and the frequency of their clinical association strengthens this belief ; but one cannot help feeling that some writers have laid undue stress upon the presence, in one or two recorded cases of the articular trouble, of symptoms which appear to be frequently associated with acute circumscribed oedema '.

I think to this group belong those cases referred to by F. E. Batten (15), 1910, as ' polymyositis in association with erythema nodosum and urticaria '. ' In erythema nodosum it is not uncommon to find the underlying muscles hard and tender to pressure ; but as the erythema nodosum clears up the affection of the muscles passes off ; in some reported cases, however, the affection of the muscles is by no means so transient. The cause of this form of myositis is obscure : cultures made from muscles gave negative results, but the association with erythema nodosum and urticaria would indicate that the poison is probably of intestinal origin.' Batten describes the symptoms as commonly affecting the lower extremities and in slighter forms coming on suddenly with severe urticaria of the skin and swelling of the muscles. The swollen muscles are painful, and any movement active or passive is acutely painful. In severer forms the lower extremities are considerably swollen and small indurated areas can be felt in the muscles. Rapid recovery is the rule, the acute symptoms pass off in a week, but some muscular tenderness may persist for a time. ' This form is prone to relapse.'

But it is in McCall Anderson's (16), 1887, account that Willan's urticaria tuberosa meets with the first complete recognition since the time of Rayer. ' There is a variety of nettle-rash to which the term urticaria nodosa seu tuberosa has been given. It is a rare affection ; it appears in the shape of pretty hard nodosities about the size of a split marble and of a reddish colour, which occur oftenest at night and disappear in a few hours, frequently recurring. They may involve any part, but the extremities and limbs are specially liable. In very rare cases they are associated with congestion, rupture of capillaries, and ecchymoses.'

Symptomatology.

The observation of McCall Anderson and Fouquet that this is a rare variety of urticaria appears to be correct. Since Willan's original description few cases are met with in medical literature. It would be of little importance if the conditions were common, easily recognized, and therefore considered too trivial to be reported. But the matter is not thus lightly to be dismissed. Although

the disease may occur more commonly than the recorded instances would suggest, the cases appear to be obscure in nature and, for the most part, to be wrongly diagnosed. Perhaps their resemblance to rheumatoid arthritis leads to their being placed in this protean group of diseases rather than amongst the urticarias where they rightly belong.

The clinical picture of urticaria tuberosa is, however, not without distinctive features. Age affects its incidence little if at all. The sex distribution shows that in common with other forms of angeio-neurotic oedema females are some-what more prone to be affected. A characteristic attack is marked by the sudden rapid development of subcutaneous or deep-seated swellings, varying in size from nodules as large as peas to tumours as big as oranges. They are multiple and distributed about the extremities, especially the fingers, hands, wrists, feet, and knees, occasionally about the loins and the back of the shoulders. These nodules rarely involve the skin, which, as a rule, shows no discoloration, but they appear to select fascia, tendon sheaths, and peri-articular tissues. The swellings are unaccompanied by a true cutaneous nettle-rash. They are hard, or, if large, may give rise to the sensation of deep-seated tense fluid swellings, pitting subcutaneously on prolonged pressure. Movement of the limbs involved may be stiff and painful. Sometimes the fingers are the seat of diffuse swelling, not situated at the joints but between them, giving rise to a fusiform appearance which resembles at first sight rheumatoid arthritis, but distinguishable therefrom by the presence of an apparent constriction over each joint.

The subjective sensations complained of, in addition to aching pain and stiffness, are tingling and burning but rarely itching. The nodules usually occur at night and disappear before morning, or they may be even more evanescent, lasting only a few hours. The patient is left weak, languid, heavy from want of sleep, and tired as if bruised. As a rule, there is no pyrexia and the pulse-rate is not increased.

Bearing in mind that the condition is commonly diagnosed as rheuma-toid arthritis or some form of chronic rheumatism, it is important to note that there is no tendency to permanent damage of the joints. There is no grating or creaking to be felt, and no rarefaction, erosion, or osteophytic growths are discovered by X-rays. The joints do not become fixed, or deformed, and in the hands no deflexion of the phalanges results even from repeated attacks.

The patients are healthy and well-nourished, ready and able to exercise as soon as the swellings have disappeared. Sometimes, indeed, exercise seems to disperse the swellings and remove the sensation of stiffness. Rubbing and even vigorous massage may actually conduce to a feeling of ease and comfort. Distension of the joint capsule with fluid does not seem to occur, although bursal effusions may be present.

Cardiac complications are conspicuously absent, so too are organic nerve lesions and wasting of muscles.

The distribution of the swellings is not symmetrical, nor does it correspond with nerve or segmental areas.

No urinary or menstrual irregularities coexist.

The blood examination reveals no abnormal cell-counts and cultures from the blood proved sterile; but there appears to be a definite delay in the coagulation-time of the blood during the attacks.

Complications and Sequelae.

No complications or sequelae have been observed. The condition seems to clear up suddenly and completely.

Gastro-intestinal disturbances, such as vomiting, colic, or diarrhoea, not infrequently precede or usher in an attack. This is the one occasional accompaniment which calls for attention.

Aetiology.

From the preceding remarks there is some probability that among the causes of urticaria tuberosa digestive derangements have to be reckoned with. Perhaps the victims have an idiosyncrasy to some particular article of diet whose identity cannot be traced and need not be the same for each individual. Or it may be that any interference with digestion leads to absorption of intestinal toxins which determine the outbreak. Exposure to cold and excessive exercise act as exciting causes, especially exposure to cold after being heated by muscular exertion. Heredity cannot be definitely established as a cause. Emotion seems to play no part. Illnesses of a debilitating nature, such as influenza and diphtheria, may in some degree account for the liability to attacks. Neuroses in a general sense are not observed in the patients.

Prognosis.

The prognosis may be summed up in a very few words.

Rapid recovery from an attack is the rule.

Recurrence is probable, and the liability to recurrence extends over many years, perhaps a lifetime.

Permanent injury does not occur.

Diagnosis.

The disease has to be distinguished from acute rheumatism, especially the modern variety in children. This should not be difficult. Pyrexia is either absent or very slight and transient. The patients cannot be described as ill, they are merely uncomfortable, unless the gastro-intestinal disturbance is very severe. The joints are really free from effusion. The heart remains unaffected. The nodules are not situated over bony prominences, as, for instance, the exposed border of the ulna.

From rheumatoid or osteo-arthritis, urticaria tuberosa may be differentiated by the fact that there is no permanent fixation of the joints and rarely any effusion into them. There is an absence of creaking, grating, or lipping of the articular end of the bones. X-rays show the joints to be normal in appearance.

The patients are not wasted or pigmented, and there is no excessive sweating of the hands. On the contrary, the skin may show a remarkable absence of perspiration. There is no ulnar deflexion or flexion of the fingers. A curious hyper-extension of the phalanges has been noticed. Heberden's and Haygarth's nodes do not occur.

From gout the diagnosis is easy. The history of the attacks presents no features of resemblance. The exquisite pain and tenderness are lacking, and the skin over the affected joints does not assume any dusky redness. Tophi are not present.

Description of Cases.

Case I. Miss L., aged 50, a lady of independent means, who had resided for many years in Australia, was seen in consultation with Dr. A. L. Flemming in June, 1909. For many years she had suffered from attacks of rheumatism, which had recently been pronounced to be rheumatoid arthritis. She had visited Harrogate and other spas considered to be useful in rheumatic affections. Inquiry elicited the fact that she had on previous occasions suffered from ordinary attacks of urticaria (nettle-rash). The patient considered that exposure to cold was the chief exciting cause of the condition, and could not definitely associate its appearance with any other circumstances. Her general health and nutrition were good. The disease manifested itself by the sudden rapid appearance of hard swellings in various parts of the body, especially upon the fingers, wrists, deltoid, and rhomboid regions. One favourite spot she pointed out over the latissimus dorsi, which she used to ask her maid to ' pummel as hard as she could,

and it would go '. The tumours usually began at night, they might be present on getting up in the morning, but they were of a very fleeting nature and would often have disappeared by the time her doctor came to see her. Exercise seemed to lead to their disappearance. The particular attack in which I saw her was characterized by a large protuberance over the back of the right wrist, which at first sight presented the appearance of a dislocation of the wrist with the bones of the forearm prominent above the dorsum of the hand. This swelling was hard, tense, and deep-seated; it did not involve the skin completely, which was not, however, freely movable over the swelling. The skin was not discoloured and did not pit on pressure; but on prolonged firm pressure a deep-seated subcutaneous pitting could be produced. The discomfort complained of was a dull aching with stiffness. The wrist-joint, however, could be freely moved without any sensation of creaking or grating. There was no effusion into the joint itself. The movements of the extensor tendons of the fingers were not limited, although the patient said they felt stiff and a slight creaking could

Spindle-shaped swelling of fingers.

be detected suggestive of teno-synovitis. The fingers of both hands presented a curious spindle-shaped deformity, which at first sight resembled rheumatoid arthritis, until it was noted that the maximum swelling of each spindle corresponded with the centre of the phalanx and a constriction occurred at each inter-phalangeal joint. There were several discrete deep-seated nodules about the size of peas, not situated, like Heberden's nodes, at the joints and about the articular ends of the phalanges, but in the length of the phalangeal shaft. These

nodules ached, but were not painful or tender to the touch. They were not
in the skin, nor did they move with the tendons, but seemed to be situated on,
rather than in, the tendon sheaths. Movement of the fingers was limited to
a slight extent by stiffness, but there was no creaking or grating in the joints
or tendon sheaths, and there was no fixation, flexion, or deviation of the fingers,
and no lipping or osteophytic formation about the joints. Similar nodules,
varying from the size of a pea to a walnut, were present in the rhomboids and
deltoids. These felt precisely like those met with in nodular rheumatism, except
that many of them were of a larger size. The patient complained of aching
and stiffness in these regions as well as in the loins and hips, where no
swellings could be detected.

A few hours later in the day Dr. Flemming again saw the patient and found
the hand quite normal in appearance, the whole of the swellings having vanished.
There was a feeling of slight malaise during and after the attack, and the patient
said she felt as if she had been beaten all over. There had been a complete
absence of the itching and burning of the skin usually associated with urticaria.
No gastro-intestinal symptoms were present. The patient had passed the
climacteric several years previously and suffered no pelvic disorders. She was
aware that she had been subject to these attacks since childhood, and expressed
her surprise that, contrary to the prognostications of many physicians, she was
developing no permanent deformity of her joints, and between the attacks which
came on at intervals, varying from a few days to many months, she enjoyed the
free use of her limbs. In the course of discussion as to the nature of her malady
she ventured the suggestion that she was the victim of ' Australian blight ',
a name then quite unfamiliar to me and of whose exact nature I am still
ignorant, save that it is given in a few books as a synonym of urticaria tuberosa.
A blood-count showed no abnormal conditions. The coagulation time of her
blood taken the following day showed a very slight delay.

The urine examination revealed nothing abnormal, and there was no evidence
of renal disease or arterio-sclerosis.

A course of treatment with calcium lactate marked a complete cessation of
symptoms, but such an interval of freedom from the attacks was not unusual
apart from treatment.

Subsequent observation of this patient has shown that she occasionally
develops spontaneous ecchymoses in the skin.

Case II. Miss A. C., aged 40, in 1908 suffered from a severe attack of
influenza, which was followed by a condition called ' neuritis ' in the arms and
hands, unattended, however, by wasting or motor weakness. The symptoms
complained of were intense pain shooting down the arms to the finger-tips, with
tingling and stiffness of the fingers ; the fingers felt cold and dead ; used to turn
very white and swollen. The attacks were singularly transient and did not
prevent her from playing croquet assiduously. This continued for three years,
but I did not chance to see her during an attack, until, in May 1911, she showed
me her hands with the fingers white and swollen, presenting a series of charac-
teristic spindle-shaped swellings over the phalanges, and constrictions at the
joints. In the flexor sheaths of the fingers were small hard nodules, which
caused aching and stiffness, but without tenderness or pain on being handled.
The joints were free from swelling ; there was no creaking, grating, or fixation.
No other parts of the body were affected.

Miss C. told me that this was the condition which during the last three years
had been variously diagnosed as neuritis and rheumatism, and for which she had
visited Continental and English health resorts famed for curing rheumatic diseases.
The attacks were always very transient, and as a rule began at night, disappearing
during the first few hours of the morning after she got up. She thought
moderate exercise and moving of the limbs cleared up the swelling. The tingling
pain before the swellings developed was sometimes intense. Her opinion as to

the causation was that exposure to cold and excessive exercise brought on the attacks. She was particularly liable to them after playing croquet during a hot summer afternoon and continuing until the colder evening drew on. Her general health was excellent; the heart, lungs, urine, and menstrual functions were normal.

She had never suffered from a true urticaria (nettle-rash), but about a year previously had developed two streaks of sclerodermia (morphoea) down the subcutaneous borders of both ulnae. This condition she had completely recovered from.

She was of somewhat massive build and led an active life, playing croquet and tennis and dancing vigorously. She came of a family which might be described as 'neurotic', though she herself displayed little or nothing of this tendency. Her digestion was good, and she was not subject to constipation or gastro-intestinal disturbance.

I was struck by the similar appearance of her fingers to that of Case I, both as regards the diffuse swelling and the nodules. She too had been told that the condition was incurable and would inevitably lead to painful crippling of her hands, a prognosis which distressed her greatly as she earned a small income by practising and teaching lacemaking. Her blood examination showed no abnormality except a marked delay in the coagulation time during the attacks.

Case III.   Elsie M., aged 11, a slightly-built girl with dark auburn hair and a freckled skin, had complained for three years of pains in the joints for which on several occasions she had been admitted to the Bristol Royal Infirmary with the diagnosis of subacute rheumatism. The case was singular from the fact that although I had seen her in the wards each time she was admitted, I could never discover any swollen joints, nor indeed anything the matter with her.

One night, however, in April 1910, her mother telephoned and asked if I would see her, and she came to my house at 9.30 p.m. with numerous nodules on her knees, elbows, and fingers. On the knees and elbows these nodules were cutaneous and subcutaneous, about the size of hazel nuts, fairly hard but pitting on firm pressure with a slightly dusky red tinge in the overlying skin. They were very painful, making movement stiff and difficult. Several nodules appeared to be attached to both patellar tendons. In the fingers there were deep-seated nodules about the size of peas, looking and feeling like ganglions on the tendon sheaths; there was no dullness or oedema of the skin. There were the same spindle swellings between the finger-joints with the contractions at the joints, which had attracted attention in the two previous cases. The swellings were said to rise about 6 p.m. every night and disappear by the morning. They were most severe when the child was fatigued by physical exertion.

Sometimes a particularly bad outburst was preceded by an attack of vomiting with or without diarrhoea. In October, 1910, she was admitted to the Bristol Royal Infirmary suffering from jaundice, apparently of the catarrhal type, at the onset of which there was severe vomiting. During her stay in the ward on this occasion the evening attacks of urticaria tuberosa occurred frequently. The patient showed a marked degree of hyper-extension of the fingers at all joints— a feature which was also noticeable in Case II, and serves to accentuate the difference between this condition and the deformities usually met with in rheumatoid arthritis. The delayed coagulation time of the blood during the attacks was pronounced.

There was no sign of organic disease, and the heart remained unaffected in spite of repeated attacks of so-called subacute and nodular rheumatism.

The attacks still continue, and are not controlled by administration of calcium salts; the patient regards them philosophically and is now very little disturbed by them.

Case IV. C. S., aged 17, a short, stout girl with a fresh ruddy complexion, whom I was asked to see early in April, 1911, with Dr. Falconar at Shirehampton.

She had been ill for six days; the attack commenced suddenly with headache, frequent violent vomiting with diarrhoea, and pains in the chest and joints, the latter becoming swollen. The temperature had on one occasion risen to 99° F. The joint pains were so severe that morphia was resorted to after failure of salicylate and other remedies.

Nine years ago the patient had a severe attack of diphtheria, after which attacks similar to the one described appeared to follow. The administration of antitoxin is probable as the child was treated in the City Fever Hospital. These attacks come on at frequent intervals, they are often accompanied by vomiting, and also signalized by painful swollen joints. Some attacks are so slight that the patient is not confined to bed. They usually come on at nights and last till the morning. Moderate movement brings relief, but a long walk or fatigue precipitates or aggravates the attack. This patient had sought relief at Bath four years previously, and after leaving Bath suffered from an attack of rheumatic fever (so called) for several weeks. She has also had influenza several times.

When I saw her she was lying in bed looking plump and rosy-cheeked and not ill, but movement caused her great pain. Her temperature was 98·4, the pulse rate 84, and the respiration rate 24.

She complained of great pain in both pectoral muscles and in the deltoids, which were extremely tender on pressure or movement; there was also pain over the scapulae and rhomboids, but there was no swelling, and no nodules were discovered in these regions.

The right elbow was enlarged by an ill-defined fluctuating swelling just external to the olecranon and not communicating with the joint. The fingers of both hands were stiff but without effusion into any joints and without nodules; the swelling was situated between the joints with constriction at the joints.

Both legs were mottled and swollen resembling a fading nettle-rash, but there had been no itching. About the middle of the left calf were two discrete deep-seated painful lumps about 1½ inches in diameter which felt in shape and consistency like soft ginger-nut biscuits. The skin over them was not reddened or infiltrated, and the nodules were apparently attached to muscle or deep fascia. They were tender and pitted on prolonged pressure, but there was no pitting of the skin. None of the joints of the lower limb was swollen. Three similar but smaller nodules were present in the calf of the right leg. In three days the condition had cleared up, but during the rest of the month of April, after admission to the Royal Infirmary, she had at intervals of two or three days attacks of severe pain, sometimes, not always, accompanied by localized swellings, and of a transient character.

About a month after leaving the Royal Infirmary the girl came to see me with a swelling over the left ankle, a typical patch of deep-seated oedema about 1½ inches in diameter, and she told me that she had had a similar swelling in the thigh pointing to the inner condyle of the femur about the inner tuberosity.

Her attacks were less severe and less frequent after this, possibly because she was more careful in her diet and regulated her bowels with magnesia.

Unhappily she died in 1912 of cerebral complications following an acute suppurative otitis media. No post-mortem examination was allowed.

Case V. Mrs. S., aged 27, the wife of a medical man with whom I was well acquainted and whose children I had frequently attended for lichen urticatus, and many curious urticarial rashes.

She had suffered for nearly two years from some form of chronic rheumatism which she had been warned would lead to crippling deformities of the joints.

I had never been consulted by her for her own health.   One day, however, I was
seeing the children for one of their numerous urticarial outbursts, and she held
out her hand saying she wished I could cure her fingers which were crippled
with rheumatism.   But the fingers were not swollen at the joints, there was
instead a constriction at each joint and spindle-shaped swellings between.   There
were two or three nodules the size of peas apparently situated in or on the
extensor tendon sheaths at a distance from the joints.   On inquiry, I found that
these were the nodes of the rheumatoid arthritis from which such dire results
were apprehended.   These nodules were sometimes attended by painful lumps
and stiffness in the small of the back and gluteal regions.

I have seen her on many occasions since suffering from the deep-seated
nodosities of urticaria tuberosa, and at rarer intervals from spontaneous bruising,
but she has never developed a nettle-rash.

Her mother is the subject of most severe nettle-rashes.

Blood-coagulation Times.

By Addis and Sabrazé's method.   Temperature 18·5° C.

Case	I.	Miss L.	.	.	.	.	. Average 8 min.
„	II.	Miss A. C.	.	.	.	.	„ 10·15 „
„	III.	Elsie M.	.	.	.	.	„ 13 „
„	IV.	C. S.	.	.	.	.	„ 10 „

Control (Egomet) varies from 6·5 to 7 minutes by the same method and taken
with each patient.

Treatment.

The essential point to recognize in the treatment of this condition is its
urticarial nature, and, moreover, to realize the exceptional disposition which
its victims display towards developing drug eruptions.

The salicylate group, colchicum, and the iodides are useless; the latter
frequently adds to their miseries.   So, too, do the bromides and chloral and
the many hypnotic drugs which are apt to produce exudative erythematous
rashes.   In the majority of attacks which I have seen in the cases described
the speediest and greatest relief has been obtained by prompt and free purga-
tion, a dose of calomel or blue pill followed by sulphate of magnesia two or
three times a day sufficient to produce one drastic purge and one or two loose
daily actions of the bowels is the only satisfactory treatment I know.

Regular administration of calcium may ward off the attacks, but it does
not appear to cut them short in the same fashion as the other alkaline earth,
magnesia.   It has the disadvantage of tending towards constipation.

Diet is of the utmost importance.   My own experience has been that each
patient subject to urticaria (of any type) is a law unto himself, and each case
must be carefully studied until by varying exclusions from the diet an optimum
is reached, where the attacks are reduced to their lowest frequency.   Speaking
generally, the plainest diet is best; milk alone during an attack is to be recom-
mended, but some of my patients have told me that the surest plan for curing
an attack of urticaria is to starve it out and live for a day or so after the
outbreak on nothing but bread and butter or toast, and water.   An heroic
remedy, but one based on sound experience and much suffering.

Conclusions.

In conclusion, one may say that the treatment of urticaria tuberosa like that of other forms of urticaria is unsatisfactory, but its correct diagnosis is of the utmost importance. A patient who is subject to attacks of urticaria tuberosa derives no little comfort and relief from the knowledge of the nature of the disease, and the reassurance that it brings no permanent disabilities in its wake. The minor discomforts of a nettle-rash may be laughed away, but the gloomy anticipation of helpless deformity from rheumatoid arthritis may spoil a life long ere the crippling has come.

The pathology and histology of these nodules cannot be proved by direct examination, as the patients are not as a rule agreeable to deep incisions into muscles and tendon sheaths for the purpose of removing tissues for microscopical examination. They are the less inclined to these methods of research from their experience of the transitory nature of the swellings.

The behaviour of the swellings leaves no room for doubt that they are of the nature of urticarial effusions or angeio-neurotic oedema.

It is regrettable that in Quincke's survey of angeio-neurotic oedemas this nodular form seems to have been lost sight of. Since rheumatoid arthritis claims Heberden's nodes, Haygarth's nodes, and osteo-arthritis, the easiest explanation of these cases of urticaria tuberosa was to throw them into the same group. Then with inappropriate remedies and a discouraging prognosis to leave the sufferer to discover that Fate was not as hard as she was painted, in fact that urticaria tuberosa was a disease differing totally in its effects and sequels from arthritis deformans, to which superficially it bears so close a resemblance.

Evidently a group exists, recognized by Willan, in which the urticaria effusion is so limited that it does not present the characteristic features of either an urticaria or angeio-neurotic oedema.

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PENETRATING WOUNDS OF THE LUNG AND PLEURA

By R. D. RUDOLF

With Plates 12–17

PENETRATING wounds of the chest are by no means always fatal, nor need they necessarily permanently invalid the sufferers. Many men are to-day serving at the front who have been thus injured, and they are apparently perfectly well. But the prognosis is not so good as in the patients who formed the basis of a recent clinical lecture by Dr. Hale White (*Lancet*, Dec. 4, 1915), in which he says that among the many cases that he has seen in hospital since the outbreak of the war he has not had a single fatal one. The evident reason for this is, as he says, that the bad cases never reach England. A certain proportion of the cases do not leave the field of battle, another portion do not get beyond the field ambulances and casualty clearing hospitals, and others again die in the base hospitals in France. The bad ones are kept in this country (France), as being too ill to stand the journey, and only those reach England who are practically already out of danger. Dr. Hale White quotes Colonel L. A. Lagarde, U.S.A. (*Gunshot Injuries*, 1914), who shows that the mortality of penetrating wounds of the chest in the French army during the Crimean War was 91·6 per cent., in the English army over 70 per cent., and among those who survived to reach hospital in the American Civil War it was 62 per cent. With the introduction of small bullets of high velocity it began to fall, and in the Spanish-American War it was 27·5 per cent., in the Boer War 14 per cent., and among the Japanese in the Mukden battle 3·67 per cent. But these extremes are hard to understand and probably are open to the usual fallacies of statistics.

It is recommended in the Official Memorandum on the Treatment of Injuries in War, issued last summer to the medical officers in France, that 'these patients should not be permitted to move for several days, but at the end of a week should be sent to the base'. And again, 'It is important that men with wounds of the lung should not be sent across the sea earlier than a fortnight after the injury. Three weeks is a safer time-limit, to guard against the risk of a fresh haemorrhage or pneumothorax.' Hence it will be realized that if a penetrating wound of the chest is going to prove fatal, the death will occur either on the spot, at the base, or at some hospital between these two extremes. Those patients who survive the first three critical weeks and, moreover, are adjudged at the base as fit for the journey to England, are by that time out

of danger of further haemorrhage and of most of the complications that haunt them at first.

Penetrating wounds of the lung and pleura are most commonly caused by rifle bullets and shrapnel balls, but also occur from pieces of shrapnel and shell. Very rarely do we see them caused by bayonet thrusts, and no example of sword wounds of the chest has yet come under our notice.

It is not intended to discuss here the classical physical signs of chest injuries. It is rather hoped that it may be of interest to illustrate certain points which have become clear and certain exceptions to the ordinary text-book descriptions of conditions which in times of peace are so rare.

As already said, penetrating wounds of the chest are by no means always fatal, and one of the first things that strikes one is what apparently hopeless wounds, judging from their anatomical positions in the chest, may give rise not only to no danger symptoms but almost to no discomfort. A man may be shot through the chest and scarcely know it at the time nor have symptoms or signs afterwards. Thus a man was shot by a sniper from about two hundred yards distance. The bullet entered the second right intercostal space close to the sternum and came out just below the angle of the left scapula. Beyond slight spitting of blood for a day or two, he had no symptoms, nor could anything be found wrong with him on physical, including X-ray, examination. He walked three miles after the wounding and only had gone to the ambulance because he 'felt wet at the back'. The wetness was due to haemorrhage. Case I is another example. Here the bullet travelled from side to side and yet gave rise to no trouble except a little haemoptysis.

Case I. Private R., aged 18. Was shot on May 11 and admitted to the hospital a week later. Was found to have a single wound. It was in the right inferior axillary region in the eighth intercostal space. It discharged some pus. Patient said that after being shot he spat some blood for a day or two, and had a little pain in the right chest when breathing deeply. No symptoms after admission. No signs of fluid or air in the pleurae. When screened a shrapnel ball could be seen in the left lung at the level of the third rib posteriorly. It danced up and down continuously, not keeping time with the heart or the respiration. In a few days the patient was sent to England (Fig. 1).

Every medical officer sees such cases, where, anatomically viewed, some vital organ should have been damaged and yet has escaped.

On the other hand, what may appear to be almost a safe wound, anatomically considered, may quickly end in death. Case II is an example of this.

Case II. Private B., aged 25. Was shot four days before admission. When admitted was still spitting blood, and had much orthopnoea. A small wound of entrance was found close to the sternum in the second left intercostal space. Wound of exit was large, and was situated over the front of the right shoulder. A straight line between the two points would scarcely go deeper than the ribs. Physical examination showed the right chest full of fluid. Patient died within a few hours of admission. The post-mortem examination showed that the bullet had passed close behind the sternum, scraping it; then slightly

in and out (by the same wound) of the pleura and just touched the lung. The right shoulder was much shattered. The pleura was full of blood, with no sign of clotting. There was no damage to the great vessels or to the internal mammary arteries. The bleeding appeared to have been from an intercostal artery.

The wound of entrance may not be in the chest at all and yet terrible and even fatal injury to the chest supervene. For example, a man came in, very ill with a bayonet wound on the abdominal surface below the ninth left costal cartilage. He was found to be suffering from an infected right haemothorax. Again, a man was shot in the right abdomen below the liver. The wound of exit was behind, over the eleventh right rib. Fluid was found in the right pleura, which proved at both of two aspirations to be pure bile. As a third example of these distant wounds of entrance one may give Case III, where the bullet entered the point of the left shoulder and did not come out. It was found in the left lung root.

Case III. Private G., aged 29. Was shot on Sept. 25 and admitted to the hospital three days later. Was found to have a small wound of entrance at the point of the left shoulder. The missile did not come out. Left arm was swollen and painful, and the radial pulse in it scarcely perceptible. In the anterior axillary region and all over the upper part of the left chest anteriorly a continuous hum could be heard and felt. It was accentuated by the pulse-beat. The heart was much displaced to the right. Upper part of the left chest hyper-resonant, and over it the breath-sounds were distant but the vocal fremitus and resonance were normal. Coin-sound here present. The X-ray showed a fracture of the head of the left humerus, a pneumo-haemothorax of the left chest, and a bullet just to the left of the heart and moving with the heart-beat. There was much fever and the general condition was bad. He died six days later, and at the post-mortem examination it was found that the axillary vein and artery were connected through a large cavity (varicose aneurism). A large haemo-pneumothorax was present. The left lung was much shattered, and the bullet lay in its root.

In these cases so far mentioned the foreign body was a bullet or ball, but the missiles most to be dreaded are pieces of shrapnel or shell, as they do more destruction, and also very frequently carry in with them pieces of clothing, and acute infection then certainly follows.

Pneumothorax.

This condition is common after penetrating wounds of the chest. Usually, but not always, there is blood as well as air in the pleura, and very commonly, but not always, infection of the pleura follows. As an example of a pure pneumothorax, one may mention a recent case where, after an in and out perforation of the left chest, there was such a large pneumothorax that the heart was completely displaced to the right side of the chest, and yet there was no fluid in the pleura even several days after the injury. Examples of haemo-pneumothorax are not common.

The pneumothorax usually happens at the time of the injury, but may occur days after it. Thus in Case IV it happened thirteen days later.

Case IV. Private R., aged 21. Received a bullet wound in the chest on Aug. 25, and was admitted to the hospital on Sept. 4. He had spat blood for two days after the injury, and had had slight fever since, as was shown by the chart that he brought with him. Wound of entrance was immediately to the right of the ensiform cartilage, and that of exit in eighth intercostal space in right posterior axillary line. These wounds were healed on admission. Physical and X-ray examination showed the presence of fluid in the right pleura up to the angle of the scapula. No pneumothorax. The fluid was sterile blood.

The patient was quite comfortable until Sept. 7, when, thirteen days after the accident, he was suddenly seized with violent dyspnoea and became cyanosed and almost pulseless. He had been lying quietly in bed when this happened. A couple of hours later, when I saw him, he was more comfortable, but still a little cyanosed and the pulse and breathing were very rapid. The heart was found to be displaced to the left, and the right chest in front was hyper-resonant and gave a marked coin-sound. He was too ill to have the back examined.

Three days later he was quite comfortable, but the pneumothorax was still present, although the coin-sound could not then be elicited. Five days later again, on Sept. 15, it was noted that 'coin-sound again present and X-ray shows both fluid and air in pleura, the former showing a wave with each beat of the heart' (Figs. 2 and 3). He was sent to England a few days later.

If the air enters the pleura from the external wound, infection with pus-forming organisms is much more apt to occur than if the wound which admits the air is in the lung.

As a rule the axiom holds good that the sudden occurrence of pneumothorax is accompanied by severe dyspnoea, as was shown in Case IV, but there are exceptions to this. Thus two cases recently came into the hospital in which immediately after the injury with large pieces of shell the men could hear the air passing in and out of the large wounds, and yet neither gave any history of shortness of breath, even when closely asked about it. Both men had complete pneumothorax, and both, of course, were badly infected. One was resected, and the other drained through the wound, which was low in the back. One died, and the other went to England. Case V is the latter one.

Case V. Private T., aged 39. Was wounded with a large piece of shell sixteen days before admission. The missile entered the back over the eighth dorsal spine, and left by a large wound below the angle of the right scapula. He spat blood at once and for days afterwards. He immediately could hear the air rushing in and out of the chest, and yet he insists that he had no breathlessness. On admission there was found to be a right pneumothorax with some displacement of the heart to the left. The wound was large, and the air entered and left it very freely. The coin-sound was heard all over the side, except near the wound, where an area could be mapped out by its absence and the X-ray showed that just there the lung was adherent to the chest wall, although otherwise the pneumothorax was complete (Fig. 4). The side was drained by enlargement of the wound, and eventually the patient got well enough to be sent to England.

As regards the physical signs of pneumothorax, the text-book descriptions mostly hold good, but the coin-sound (bell-sound) is very elusive. In many

cases it is not present at all, although the diagnosis of pneumothorax is confirmed by the X-ray. In others it comes and goes. Thus in Case IV it was present immediately after the occurrence of the pneumothorax, was absent three days later, and again was noted five days after that. This point, the elusiveness of the coin-sound, one notes frequently in pneumothorax produced artificially as a therapeutic measure. One might be tempted to believe that it was most apt to be present when the pressure of the air in the pleura is the same as that of the atmosphere, as it is always found when there is a free opening in the costal parietes (as in Case V). In another similar case to Case V, where there was a large opening in the chest wall, it was always present, even being there after death. But against this theory of atmospheric pressure is the following case (Case VI):

Case VI. Driver B., aged 30, was run over by a heavy lorry and lay for nine hours unconscious before being brought to hospital. He was found to have numerous bruises over the head and legs and one of the right chest, where a broken rib was suspected. The X-ray, however, showed that there were no ribs fractured. He had a complete left pneumothorax with marked displacement of the heart to the right. Over the left chest the percussion note was almost dull, the breath-sounds were nearly absent, but the vocal resonance and fremitus, as usual, were about normal. A very marked coin-sound was obtainable all over the left chest. Patient had never had any lung trouble. The air was slowly absorbed, no fluid occurred in the pleura, and in three weeks the patient went to England practically well.

Here the air in the pleura was under such pressure that the percussion note was almost dull, and yet the coin-sound was unusually well marked. Lastly, one often hears it in a partial pneumothorax, where the air is evidently under negative pressure.

The percussion note is usually hyper-resonant, but may, as in Case VI, be almost dull, where the air is under pressure.

The breath-sounds are always very distant and vesicular, with one exception; that is, where there is a large opening into the collapsed lung. Here the type of breathing may be most characteristically amphoric and often very loud.

The vocal fremitus and resonance are usually present to about the normal extent, and the latter may have a resonating tone which is very special in character.

Tinkling râles are sometimes heard, of a peculiarly musical character. Hippocratic succussion can easily be elicited where fluid also is present, but as a rule the patients are too ill to permit of the shaking.

In most cases of pneumothorax, where the air has come from the lung and infection is absent or not severe, the air is absorbed with a rapidity that greatly varies. In those instances where the air has come through the chest wall, and especially where the opening remains, infection is nearly always a sequence and the case becomes one of pyo-pneumothorax, and the only hope is free drainage.

Fig. 5 is a good example of a partial pneumothorax. Adhesions prevented

the upper part of the lung from collapsing. The air was under such pressure that it gave an almost dull note. The lung was greatly compressed upwards. The heart was displaced to the right.

Haemothorax.

The bleeding here usually is from the lung, but may, as in Case II, be from a vessel in the parietes. In nearly every case the haemorrhage has stopped before the patients reach us at the base, but we have had two instances of death from this cause alone. Probably medical officers at the front could tell a very different tale.

All cases have some fever at first, and this may last for many days without there being any infection to account for it. The removal of the bulk of a haemorrhagic effusion may cause the temperature to drop to normal almost as if an abscess had been opened.

As already mentioned, the greatest danger that threatens these cases is acute infection of the blood in the pleura.

Thus all cases may be conveniently divided into infected and non-infected ones. Sir John Rose Bradford says that 25 per cent. of their cases were infected, and this would be about the results found in our smaller series.

The infection may be received from the lung, from the skin surface, or from a foreign body carried in with the missile. The last two classes are by far the more serious, and probably should all be treated surgically and freely drained. An apparent exception to this rule, however, recently occurred (Case VII), where the blood was infected with a streptococcus, and yet the case did well after replacement of the fluid with oxygen.

Case VII. An officer, aged 22. Was seen in consultation at a neighbouring hospital. Patient had been shot in the chest two weeks before. He spat blood for two days, but had no special pain or dyspnoea. Was quite comfortable as long as he was propped up in bed. He could not lie at all on the right side. Temperature ranging about 100°. The wound of entrance was in the second left space close to the sternum. The missile did not come out, nor was it detected with the X-ray. The left chest was dull as high as the third rib in front and the spine of the scapula behind. The dullness did not shift, and there were no signs of a pneumothorax. The heart was displaced to the right, so that the right border was 3½ inches from the middle line. A small quantity of the fluid from the chest was drawn off and found to be sterile blood. A week later (that is, three weeks after the injury) we aspirated the left chest in the eighth space behind, and at the same time admitted oxygen through the third space anteriorly. 62 oz. of fluid were removed and 1,250 c.c. of oxygen admitted. There was no discomfort to the patient during the operation. The fluid was dark brown and was still fluid at the end of two days. It contained 400,000 red cells and 5,000 white ones per c.mm. It was found to contain streptococci in all the cultures and also the direct smears. No staphylococci were found, which is in favour of the belief that the growth was not due to any contamination. We expected that there would be trouble in the chest, but none occurred, and the patient went to England two weeks later and has since written that he feels quite well and is soon to be 'boarded' with the idea of returning to active service. The foreign body must still be in the chest.

The physical signs of haemothorax are, generally speaking, those of fluid in the pleura. More frequently than in the case of clear fluid, however, the characteristic lessening of the breath-sounds is replaced by tubular breathing, which would rather suggest consolidation of the lung than fluid. The displacement of the organs, the character of the upper margin of the dullness (it does not follow the margin of the lobe), and the lessening of the vocal fremitus and resonance usually make the diagnosis an easy one, and a needle will nearly always settle the point. If this is used with careful aseptic precautions there is no added risk. It should be of large calibre. Occasionally, however, the blood has clotted *en masse* and it will then not be possible to draw any off. When a specimen of the fluid is withdrawn it should always be examined bacteriologically and a culture made from it. This is the chief object of doing the puncture and should never be neglected.

The condition of massive collapse of the lung is very apt to lead to mistakes in diagnosis, and fluid may be thought to be present when none is there and the mistake only is found when the dullness very quickly clears up. This condition was well described by Pasteur (*Brit. Jour. of Surgery*, April, 1914) before the war, and examples of it are not uncommon. Over the affected portion of lung the note is dull and the breath-sounds may be distant or absent. The chief distinguishing point is that in collapse the neighbouring organs are drawn *towards* the dull area. The condition is most apt to occur when there is a wound near the diaphragm. Sir John Rose Bradford recently described a case to us where this condition existed on the left side and the only wound was a penetrating one of the right chest.

The diagnosis in all our chest cases is controlled by the X-ray, usually both the screen and plates being employed. The patient should always be photographed (unless his condition be too serious to permit of it) in the vertical posture. This does not only apply to cases where there is air as well as fluid in the pleura, but also where there is only fluid.

Fluid in the pleura shifts its position markedly in different postures, so that when the patient is skiagraphed in the horizontal posture it may appear as if the pleura were full of fluid, while, if he be then photographed in the sitting position, it will be seen that perhaps the chest is only half full. Figs. 6 and 7 illustrate this well where no air was present, and Figs. 2 and 3 where there were both air and blood.

To repeat, a photograph of a chest in the horizontal posture alone gives one no idea of the amount of fluid present in a pleura. Of course, this remark applies with much greater force when air as well as fluid is present, for in this case the pneumothorax may be missed altogether.

Extravasation of blood into the parietes has more than once led us to a wrong diagnosis of fluid in the chest. And the presence of haemoptysis here aids in the mistake. As is well known, spitting of blood often occurs after injuries to the chest wall without any perforating of the lung tissue. The lung is bruised by the sudden momentary pushing in of the ribs.

As regards the treatment of sterile or mildly infected cases of haemothorax, if the amount of blood be small, say not reaching above the angle of the scapula, and there be few or no symptoms of infection, the case may well be left to nature.   This is the character of most of the cases that pass through our hands here; they are merely kept very quiet, and at the end of two or three weeks from the time of the wounding are sent to England, always travelling as 'stretcher cases' the whole way.   There they nearly all do well, as is shown from Dr. Hale White's paper.   The blood is slowly absorbed, more slowly than is serous fluid, as it is more or less coagulated.

Where the bleeding has been greater than this and there is displacement of the heart, then something more than expectant treatment seems to be called for. If not, then there will be at the best a very long and weary convalescence, and the heart may never regain its normal position.   Also, as long as there is blood in the pleura, danger of infection haunts the patient's footsteps.   Hence the general opinion that the fluid should be removed.   There are several ways in which this may be done.

(a) The pleura may be aspirated at one sitting, and as much fluid as will come away withdrawn.   This is done by some workers, but when one thinks of the wounded lung expanding suddenly to fill the space in the chest till then occupied by the fluid, it seems an unwise thing to do if it can be avoided. Dr. Hale White says, 'In one case which I saw there was strong reason to suspect that too rapid emptying of the chest led to a pneumothorax from the tearing open of the wound in the lung'.

(b) Others advocate several small aspirations, in order that this sudden expansion of the wounded lung may be avoided.   This is better, but of course it is hard on the patient to thus subject him to several operations.

(c) The third method used is the one of removal of the fluid and at the same time replacing it with a gas.   This replacement with a gas has for its object the prevention of the rapid expansion of the lung as the fluid is being withdrawn.   A temporary pneumothorax takes the place of the fluid and the lung remains collapsed.   Then, as the gas is slowly absorbed, the lung gradually expands and all the dangers due to too sudden expansion are avoided.   Replacement with gas being the general object, there are some differences in the technique used by different physicians.   Thus Sir John Rose Bradford and his fellow-workers use only one needle, through which the blood is removed for a little while and then gas is allowed to flow in, and so on alternately until all the blood has been removed and replaced by the gas.   I have always used two needles, and through one the fluid is removed and through the other the gas enters, and thus the alternate expansion and collapse of the lung during the operation are avoided.   A large-sized aspirating cannula is introduced into about the eighth space near the posterior axillary line and is either connected with an aspirator or simply with a long tube, which has previously been filled with sterile normal saline and clamped.   This tube leads to a vessel placed at a lower level than the chest.   As soon as the needle has been introduced,

the clamp is removed and the blood siphons off. At first it runs freely, but soon begins to lag, and then the small cannula of the artificial pneumothorax apparatus, which has previously been or is now introduced into the third intercostal space in front, is opened and oxygen is allowed to enter the pleura. At first it is better to allow this to enter under some pressure in order to prevent a possible influx of the chest blood into the cannula. Then either the oxygen may be continued, or one may switch on nitrogen, or very conveniently simply filtered air, and thus continue until the end of the proceeding. As soon as the gas enters, the fluid runs more freely, and any signs of distress—such as coughing—that may have begun to appear are at once relieved, and the operation continues until all the blood is removed. It is never attempted to put in as much gas as there was fluid in the pleura, as the fluid has been under considerable pressure in most cases and there has been a displacement of the mediastinum and its contents, and it is not necessary to continue this displacement, but merely to prevent the damaged lung from fully expanding. It is best to leave about 1 cm. of positive water pressure in the chest. This is, of course, gauged by the manometers connected with the tube admitting the gas.

The chest is X-rayed before and at intervals after the replacement, and it can be seen that the partial pneumothorax is quickly got rid of by the absorption of the gas. The speed with which this occurs varies enormously in different cases. Cases VII and VIII are examples of this method of treatment.

Case VIII. Private M., aged 22. Had been shot ten days before being seen with the medical officer. Small healed wound of entrance near angle of left scapula. Shallow larger wound of exit to right of spine at a lower level. There had been slight spitting of blood for a day or two and slight fever. Now temperature practically normal and little discomfort. The whole of the left chest found to be dull on percussion and heart displaced to right nipple line. Over the dull area the respiration was feeble and the vocal resonance and fremitus much decreased. A specimen of fluid drawn off was found to be sterile. On Aug. 14 (fourteen days after the wounding) he was aspirated, or rather siphoned, and 52 oz. of bloody fluid removed. At the same time 450 c.c. of filtered air were allowed to flow in through the fourth space anteriorly. There was slight coughing at first, which ceased as soon as the air was admitted. More gas might have been put in, but it did not seem to be necessary as the patient was so comfortable. Next day the heart was almost back to its normal position, and the left chest was resonant except for a slight amount of partial dullness below the level of the scapula. The diaphragm could be seen with the screen to be free from fluid and to be moving well. The patient left for England a week later feeling quite well. Fig. 8 shows the chest before, and Fig. 9 after, the aspiration.

Sometimes the blood cannot be removed, owing to massive clotting, but this is rare. Case IX is an example of it, however.

Case IX. Private D., aged 28. Was first seen with the medical officer on Aug. 10, eleven days after the infliction of the wound. The wound of entrance was in the left chest behind, just internal to the spine of the scapula. There was no wound of exit. There was a good deal of pain and tenderness over the seventh and eighth left ribs in the axillary line, but no fracture or foreign body

was discovered here. There was almost no fever, and the patient was fairly comfortable while keeping quiet in bed. The left chest was completely dull, and the X-ray confirmed the diagnosis of a large haemothorax. A small quantity of sterile blood-stained fluid was withdrawn, but when, four days later, we attempted to aspirate the chest nothing would flow, although the large needle was inserted in various directions. It was concluded that the bulk of the blood had clotted in a massive manner. The patient went to England a few days later.

The introduction of even a small amount of gas relieves the patient at an aspiration very much. After the aspiration sometimes of only a certain amount of the blood, absorption of the remainder takes place very rapidly, although before the operation absorption seemed to be at a standstill. The same thing is seen in pleurisy with effusion, only to a much greater extent.

The little operation is always done under local anaesthesia, and it is wise to let the patient have $\frac{1}{4}$ grain of morphia half an hour before. After the removal of the blood the heart often takes a long time to return to its normal position. This is not always the case, but is the rule. This point was referred to by Dr. Hale White, and it has also been our experience. Thus, in a case where 84 oz. of bloody fluid were removed from the left chest at one sitting with very little entry of gas, the heart, which had been out to the right nipple line, remained there after the operation, and at the end of two weeks, when the patient, who was otherwise very well, had an almost empty left pleura and no pneumothorax, it had only come in an inch. No reason could be detected through the screen as to why it remained there. The aspiration was done twenty days after the infliction of the wound. On the other hand, as in Case VIII, the heart may come in almost at once, and in Case VII it was completely back in a week. Probably the heart will always return in time to its normal position, although our experience in France does not permit of our following the cases long enough to be sure about this point.

In a few cases, as already said, the blood may coagulate in a massive way in the pleura. In most instances, however, it remains at least largely fluid and can be mostly removed. Major T. R. Elliott and Captain H. Henry, working in Boulogne, have endeavoured to prove that coagulation occurs in every case. They state that this clotting is unlike that which occurs outside the body, in that the red cells do not remain completely entangled in the clot. According to them, the blood may (*a*) clot in a massive way, (*b*) in dense fibrinous laminae on the pleura, (*c*) as a finely shredded clot which will pass through a needle, and (*d*) as a uniformly viscid fluid which will only with difficulty pass through the needle. The blood acts as an irritant, and in most cases there is a pleurisy set up and part of the fluid in the chest may be due to that. Certainly some change usually takes place in the blood, so that this may remain fluid in a test-tube for days after its removal from the pleura; but, on the other hand, this may not be the case, and the fluid may clot just as normal blood does. Thus the pathological reports of two cases where we removed fluid have just come to hand. The one reads thus: 'Fluid port wine colour and contains numerous erythro-

cytes. Polymorphonuclear cells 49 per cent., lymphocytes 50 per cent. No micro-organisms present. The specimen was still completely fluid at the end of ninety-six hours.' The other one reads : 'Fluid completely coagulated in test-tube half an hour after removal. Sterile.' In the first case the specimen was taken eleven days after the infliction of the wound, and in the second seventeen days. Again, in Case II there was no sign of clotting in the contents of the pleura. This patient had died on the fourth day after the injury. I have not the least doubt but that Major Elliott and Captain Henry are right in the vast majority of cases—their work is beyond criticism—but the practical point appears to be that in the majority of cases of haemothorax the fluid can be largely removed by aspiration through a good-sized cannula.

It is not at all uncommon to find a pneumonia develop on the opposite side of the chest from the haemothorax. We have had several examples of this.

Haemo-pneumothorax.

In regard to these fairly common cases, I would merely remark again that no idea of the relative amount of fluid and air can be obtained from the X-ray examination unless the patient be examined in the sitting posture. The pneumo-thorax may be completely missed if this is not done. Figs. 10 and 11 show this well, as do also Figs. 2 and 3.

Many of these cases are septic and call for a resection of rib and free drainage. When they are not septic, or the infection has come from the lung, then they usually do very well and the air is rapidly absorbed.

We have not found it necessary to aspirate any case of pneumothorax yet, although, if there was any distress from pressure, it would be the right thing to do.

Wounds of the Lung.

A bullet may, as stated, pass clean through the lung without producing any lesion that can be detected by physical or X-ray examination. Usually, however, there is at least some haemoptysis. I have no undoubted case in which this has been absent, although there are such on record. Usually such a perforation of the lung is followed by more or less bleeding into the pleura, and often by some escape of air into it as well. In very rare instances, as already said, there may be a pneumothorax without any haemothorax.

Again, a bullet may lodge in the lung tissue and yet give rise to no symptoms and signs after the first few days, and may then only be revealed by the X-ray. In one such case the patient had spat a little blood for a few hours, but had no other symptoms. There was only one wound, and so it was evident that the missile must be inside, and yet most careful physical examination failed to detect anything wrong with the chest. The X-ray, however, revealed a bullet lying in the upper lobe of the right lung, and only a few days later could a few crepitations be detected near where we now knew that it lay.

Of course, when a haemo- or pneumothorax occurs, the lung collapses in proportion to the amount of fluid or air in the pleura, such collapse only being limited by the very frequent old adhesions that may exist. The extent of these adhesions, as mentioned in connexion with Case V, may sometimes be detected in a pneumothorax by the absence locally of the coin-sound.

In many instances the passage of a bullet through the lung sets up haemorrhage into the lung tissue, and this produces a massive consolidation; or a true pneumonia may follow the local lesion, although this is rare. Sometimes the passage of a bullet through the lung produces much more laceration of the lung tissue than might be expected. Then, if this is infected, an abscess may occur in the track. Case X is an example of this.

Case X. Private F., aged 25. Seen at a neighbouring hospital. He had been shot (sniped) through the chest two weeks before. He spat blood at once and for several days afterwards. The bullet had gone right through the left chest. Clear sterile fluid had been found in the left pleura several days before I saw him and it was aspirated. Three days later the side was dull again and 1½ pints of fluid were withdrawn. This time the fluid was semi-purulent and swarmed with streptococci. On examination the left chest was found to be hyper-resonant anteriorly and the heart markedly pushed to the right. Behind there was dullness to the angle of the scapula, and over the dull area the respiration was tubular and the vocal fremitus and resonance were increased. There was much fever present. A diagnosis of pneumonia about the track of the bullet was made. The patient got worse, with signs of sepsis, so a few days later the lung was explored by Major Turner and an abscess found in it, which was freely drained. The temperature rapidly dropped and the patient made a good recovery, which was only retarded by the occurrence of a phlebitis in a femoral vein.

When the lung is traversed by pieces of shell or shrapnel the laceration is very extensive, far more than would be expected from the size of the foreign body. In many cases the missile carries in with it pieces of clothing, which are found at operation, or very likely at post-mortem examination. Sepsis being now almost certainly present, these cases usually do badly and their only hope is free drainage.

In these rather desultory remarks upon perforating wounds of the chest the subject has been considered from the physician's point of view. The cases are ones in which the physician and the surgeon must work in constant touch.

The X-ray photographs of the cases mentioned here were taken by my fellow-officer, Captain J. D. Morgan, but this officer did far more than merely take photographs. He and I were in constant consultation over the cases, not only as to what and in what manner the pictures should be taken, but also over the interpretation of the findings, and if it had not been for the constant assistance that I received from this officer, any little value that this communication may possess would have been largely missing.

As will be understood, no figures or statistics can at present be given, as such are contrary to military regulations.

DESCRIPTION OF PLATES.

PLATE 12, FIG. 1 (Case I).   Shrapnel ball in left lung.   Wound of entrance was in the right lower axillary region.   Plate behind.

PLATE 13, FIG. 2 (Case IV).   Right haemo-pneumothorax.   Patient horizontal and plate posterior.

FIG. 3.   Same patient as in Fig. 2, but sitting up and plate anterior.

PLATE 14, FIG. 4 (Case V).   Right pneumothorax.   Adhesion round wound indicated by arrow.

FIG. 5.   Localized pneumothorax.   Air under much pressure, displacing heart to right and lung upwards.   Plate posterior.

PLATE 15, FIG. 6.   Fluid in right pleura.   Patient horizontal and plate posterior.

FIG. 7.   Same case as in Fig. 6.   Vertical with plate anterior.   Note curved upper margin of fluid.   Compare with Fig. 3, where there was air as well as fluid present.

PLATE 16, FIG. 8 (Case VIII).   Large left haemothorax.   Patient horizontal and plate posterior.   Heart shadow displaced to right.

FIG. 9.   Same case as in Fig. 8 after aspiration.   Heart shadow less displaced.   Patient and plate in same position as in Fig. 8.

PLATE 17, FIG. 10.   Right haemo-pneumothorax.   Patient horizontal and plate anterior. Note uniform shadow.

FIG. 11.   Same case as in Fig. 10.   Note widening of intercostal spaces on affected side.
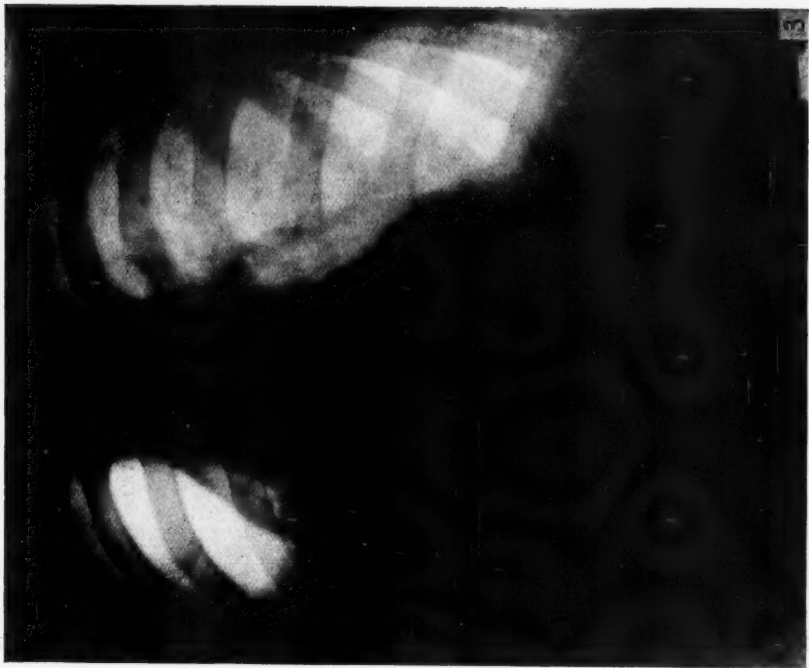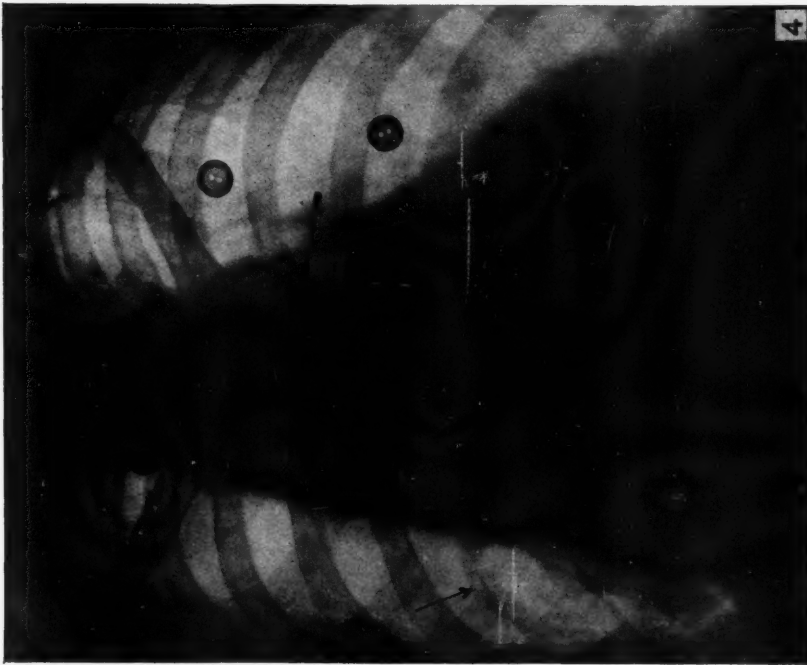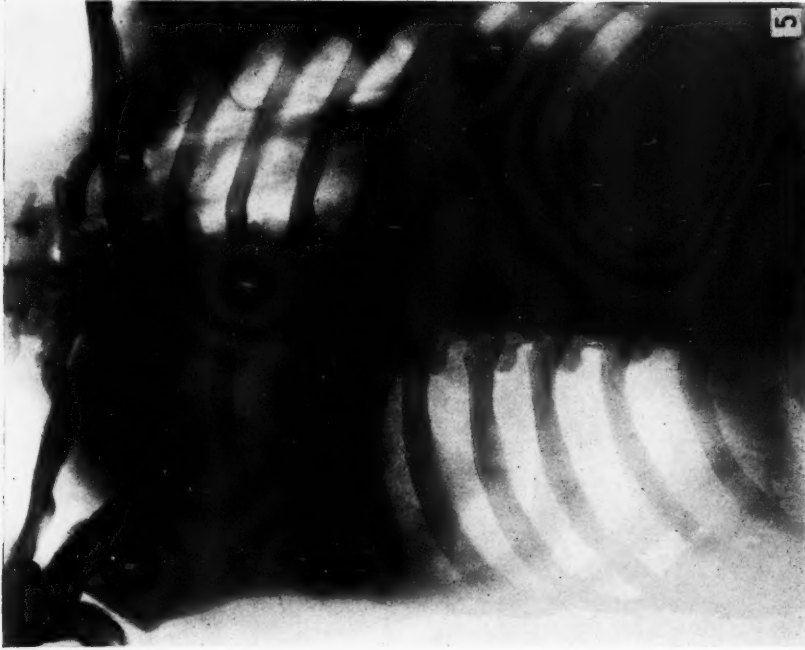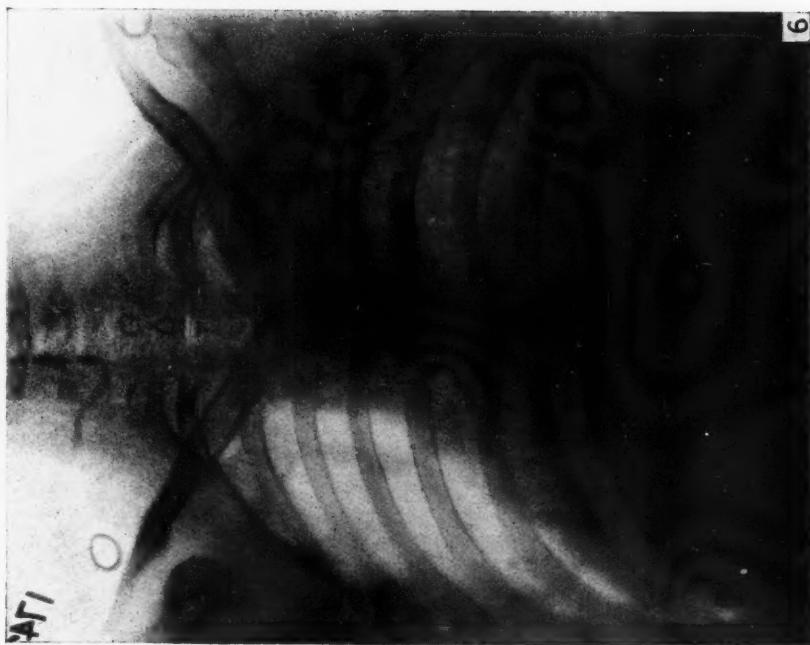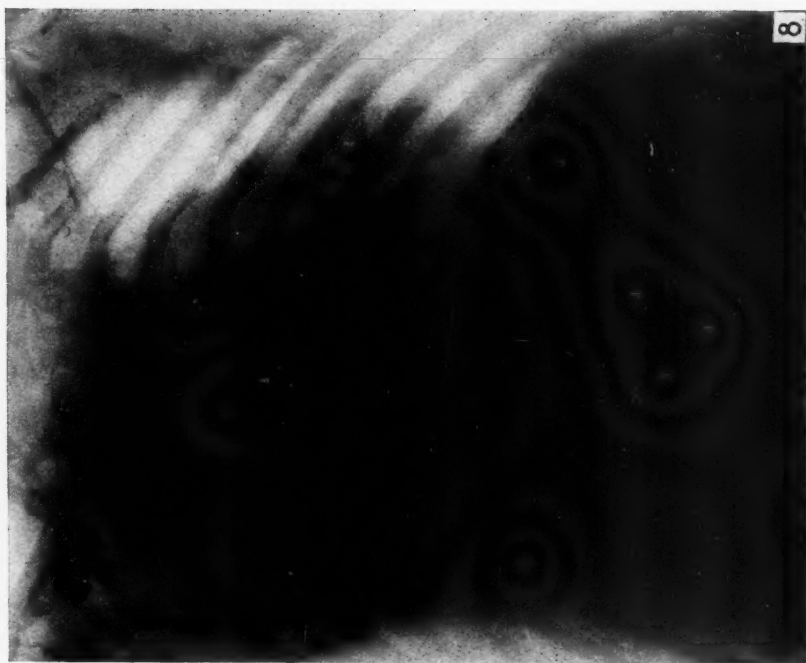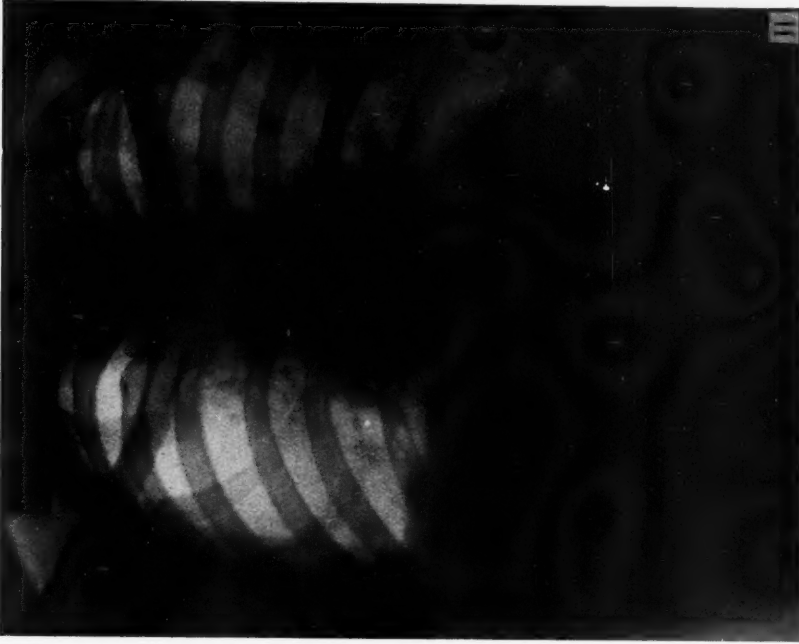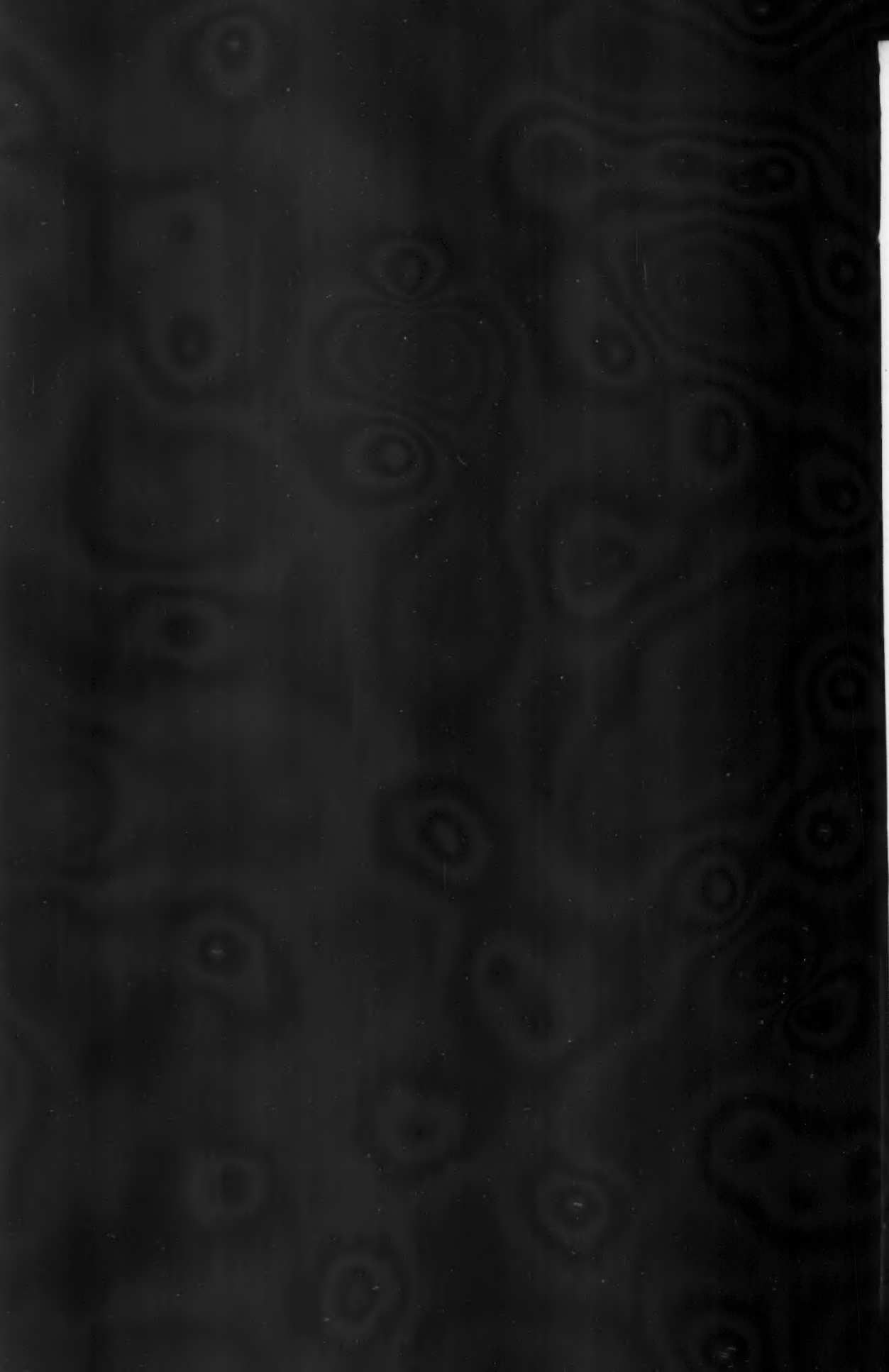
RESEARCHES ON THE PERFUSED HEART

SOME FACTORS OF THE CARDIAC MECHANISM ILLUSTRATED BY REFERENCE TO CERTAIN ACTIONS OF BARIUM AND DIGITALIS

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With Plates 18–21

Introductory.

In barium salts and digitalis we have two substances which, judged by the methods customarily employed by the pharmacologist, exert similar actions upon the heart. This similarity is not, however, adequate to permit of the one substance replacing the other as a therapeutic agent. And in the experiments below it will be shown that the modes of action of the two substances are entirely different, inasmuch as the one substance appears as the modifier of a factor concerned in the maintenance of normal cardiac excitability, and the other as an imperfect substitute for that same factor.

The discrepancy between former experimental and the clinical results is dependent in some measure upon an insufficient recognition that the cardiac mechanism, like other mechanisms, is in two main parts—the actual machinery itself, and the accessories. Thus, for example, while the transmission of the forces generated in an ordinary petrol motor depends on parts made of strong metal, adequate lubrication is an important accessory in obtaining an economic utilization of those forces. And when any such motor shows evidence of 'loss of power' it becomes an important matter to determine the cause of that loss. Thus, suppose an engine not running at full power to begin to flag because of under-lubrication; the symptoms presented by that trouble could be immediately overcome either by opening wider the throttle or by attending to the lubrication. But the end-effects of the two remedies would be vastly different; for the one would further impair the mechanism, and the other would tend to preserve it.

In the case of the cardiac mechanism, however, the finding of an increased amplitude of contraction taking place under the influence of a drug is generally sufficient to lead to the classification of that drug as a cardiac stimulant. There is insufficient realization of the possibility that any such increase of contraction may be accompanied by damage to the cardiac mechanism. Yet, as I have found,

a number of drugs do act in this way.   One of them is barium.   On the other hand, some drugs act as cardiac lubricants.   One of those is digitalis.

The work given below on digitalis and barium forms part of material, part of which has already appeared elsewhere (5–14), directed towards ascertaining the mechanism of the excitation processes.   The method employed has been roughly that of attempting to express the action of some substance foreign to the animal body in terms of something normally present.   For example, the anaesthetics, with the possible exception of alcohol, are to be regarded as substances foreign to organisms.   Their anaesthetic action, as I have shown elsewhere (6), can be expressed in the statement that they reduce the working efficiency of calcium.   Such reduction may be bound up with solution of anaesthetic in lipoids, &c., but the end-result is as stated above.   An anaesthetized heart behaves as one immediately perfused with a solution of reduced calcium content.

Employing those methods, it has been found that what may be termed the ' working parts' of the cardiac excitation processes, on which continued cardiac action depends, reduced almost to their lowest terms, are represented by certain colloids and the constituents of Ringer's solution.   The manner in which those parts interact, however, has been the subject of much controversy, the two chief antagonists being Loeb (19) and Howell (18).   The key to the controversy is given, I believe, in a former paper of mine, in which the existence of a twofold relationship between calcium and sodium was shown.   And the evidence given in that paper, together with other material on the refractory period, enables the presentation of what I believe to be a better view of their mode of interaction, in terms of a modification of Macdonald's theory of propagation in nerve. According to him, ' in the excited nerve the protein aggregates are agglutinated to form aggregates of greater individual size ; . . . this change is due to the reception of a negative electric charge.   As a result of this (potassium) salts are liberated which charge the next segment of nerve negatively, and so excite it and leave the original segment a positive charge.   This positive charge determines a return of the colloids of the original segment towards their former state of aggregation ' (20).

The theory requires, I think, two modifications, viz. that it is calcium plus the negative charge which determines the coagulative change, and that it is sodium plus the positive charge which brings the colloids back to their original state. And remembering that excitability depends on the two factors of calcium tension, and the ' state' of the excitable tissue (4), it will be seen that whether a tissue be rhythmic or not depends on the extent of the ' return '.   If the sodium can carry the ' return ' far enough, a point is reached where the ' state ' conjoined with the calcium tension is adequate to start another cycle.   If, however, the ' return ' does not reach that point normally, we get a quiescent tissue requiring some electric charge or the influence of an element like sodium to bring its power of reaction to calcium up to that point at which it reacts to the calcium tension of its environment.

What may be emphasized about the mechanism is that it represents cardiac activity as a reaction of the heart to its environment. The stimulus to contraction comes from without. The capacity to react appropriately to that stimulus lies within.

Such apparently is the normal mechanism. We may at once postulate for a normal mechanism that evolution will have determined an optimum power of interaction among its components. There can be no efficient substitute for any one of the working parts. The normal machinery, however, does require lubricating, and of its natural lubricants attention may be drawn to adrenin. A trace of this substance greatly increases the working efficiency of calcium (12, 13). On the other hand, when a heart is perfused with Ringer's solution it lacks lubrication. The calcium has now to do its work 'on its own', so to speak.

Bearing that mechanism in mind, the work below presents digitalis as a cardiac lubricant, and barium as an imperfect substitute for a working part.

Method of Experiment.

The experiments have been carried out on the hearts of *Rana temporaria* perfused *in situ* through the inferior vena cava. Full particulars of the technique are given in papers published in the *Quarterly Journal of Experimental Physiology* (5–9). In connexion therewith it may be mentioned that in the perfusion the heart wall is bathed inside and out, a fact that may have some importance when the results obtained by Poulsson (22) are considered. He found barium salts had an apparently different action according as they were dropped on or perfused through the heart.

The maximum contractibility 'C' of every heart was determined at some period in its experimental history ; sometimes at the commencement, but usually later (4).

The references given are such as immediately pertain to the point under discussion, since the paper is not concerned with describing new actions of barium and digitalis, but with an attempt to refer certain already-ascertained actions to a normal constituent of the cardiac environment. Adequate references to the literature of barium and digitalis are given by Cushny (17) and Schedel (25).

The materials used in the present experiments were the barium chloride of Kahlbaum and the crystalline digitalis (digitoxin) of Messrs. Burroughs & Wellcome.

Results.

The action of the digitalis preparation may be first considered. This was summarized in a former paper (4) under the statement that digitalis increased the response of the heart to calcium. This was ascertained by observing :

1. Changes in the amplitude of the beat of the heart when perfused with a solution containing a given amount of calcium, or noting the amount of calcium required to evoke the activity of a given proportion of the whole contractile material.

2. The amount of tonus produced by a given amount of calcium, or the amount of calcium required to produce a given amount of tonus.

3. The amount of shortening of the refractory period produced by a given amount of calcium before and during treatment of the heart with digitalis.

In every case the result was the same; a given amount of calcium had more action on each function after the heart had been treated with digitalis than was the case before; or, expressed differently, the exercise to a given degree of the functions mentioned above requires the presence of a less amount of calcium in the perfusing solution when the heart is under the influence of digitalis than is the case when the digitalis is absent. The increased responsiveness to calcium persists in presence of the drug, and also some time after its removal from the perfusing solution. To the last fact I ascribe some degree of importance.

Elsewhere (8, 9, 10) I have described two modes of reaction of the heart when exposed to the influence of drugs, &c. The one mode has the dominating characters of appearing apparently simultaneously with contact of drug and heart, and disappearing immediately after the perfusing solution containing the drug has been replaced by one without it. The second mode shows a definite time factor both in the development of the change induced, and especially in regard to its subsidence subsequent to removal from the perfusing solution of the modifying substance inducing it. The change is subsequently maintained for some time in presence of a perfusing solution not containing the substance originally giving rise to it. Changes of the first type I have termed ' surface ' changes, on the assumption that they are the immediate result of absorption phenomena taking place on the surface of the muscular colloids mediating the functions found modified; changes of the second type have been called ' deep ' changes, on the assumption that they involve changes in aggregation, or of chemical composition, in the same colloidal bodies in which changes of the first type take place.

The change induced by digitalis in the heart was thus a ' deep ' change. The alteration always took place whether the heart was a vigorous organ or a relatively feeble one.

Clark (15) has found that the action of digitalis in sending the heart into the systolic state depends on the calcium salts in the perfusing solution. Now, as is well known, it takes a greater concentration of calcium salts to induce marked tonus than it does to maintain good spontaneous contraction. Thus, if a heart be beating well on a physiologically-balanced solution containing 0·02 per cent. $CaCl_2$, say, an increase in the calcium content to 0·1 per cent. or 0·2 per cent. $CaCl_2$, say, is usually followed by well-marked tonus. By treating a heart with digitalis it is easy to get a five or tenfold increase in its

response to calcium, so that whereas when the experiment is begun the concentration of calcium present in the perfusing solution may be such as is just adequate to maintain good spontaneous contraction, yet by the time the heart has come under the influence of digitalis that same concentration of calcium becomes adequate to induce marked tonus and send the heart into the systolic state. For if the amount of calcium in the solution be greatly reduced the contracted heart relaxes and resumes good spontaneous activity. But the amount of calcium in that solution would now be such as would just have enabled the heart to maintain a scarcely recordable, or, perhaps, not recordable beat in absence of the digitalis. The heart which has been sent into the systolic state by digitalis has not been killed by the drug. It does not 'die in systole'. It has had its relations to the perfusing solution altered so that the latter is no longer a suitable medium for enabling it to manifest its more usual activity. Change the composition of the perfusing fluid and the more normal activity of the heart can be again observed.

There are two chief factors to be considered in relation to the action of digitalis, the state of the heart and the tension of calcium in the perfusing solution. Thus, an experimenter may perfuse a fresh heart with a physiologically balanced solution of the composition he thinks best or chooses to use, and find a concentration of digitalis easily adequate to induce systolic arrest under those conditions. But, if he now take a second heart and perfuse it for some hours with that same modification of Ringer's solution until the beats are small or barely perceptible, the addition to the perfusing solution of the same amount of digitalis as in the first case caused stoppage of the heart in systole is in the second case followed by a restoration of the contractions towards their original amplitude, with probably no tonus increase. At the time of treating with digitalis the two hearts just mentioned, their 'states', as expressed by their degree of response to calcium, differed, and with that difference there was a difference in the phenomena immediately manifested on treating them with the same concentration of drug. Yet the two phenomena were essentially similar in type. In both cases there was an increase in response to calcium under the influence of the drug. But whereas in the one case a tenfold increase, say, in the response to calcium was sufficient to enable the calcium to evoke the systolic state, in the other it enabled a feebly beating organ to beat much better.

The Antagonism between Digitalis and Calcium.

The actions of calcium assisted by digitalis are the surface actions of that element. Calcium has also a 'deep' action which is opposed to these. Hence there should also be an antagonism between calcium and digitalis in regard to the state of the heart induced by each. The antagonism exists and is shown in Fig. 2.

If quantities of the crystalline digitalis (0·001 per cent.), such as added to an ordinary Ringer induced systolic arrest, were added to a similar solution but containing much more calcium (0·15 per cent.), the perfusion of that solution was not followed by systolic arrest. Its perfusion for one hour was instead followed by a great slowing in rate and a decrease in the amplitude of the spontaneous contractions. At the end of that time the calcium salts were removed from the perfusing solution. With their removal a rapid failure of the spontaneous contractions ensued, and also, it will be noted, some quickening of rate. Only a few seconds were occupied in the failure, but during those few seconds the digitalis was able to induce changes in the heart, such that on reintroduction of the calcium salts the systolic state immediately came on. The only factor varied in the experiment was the calcium content of the perfusing solution. When the high calcium content was first present there was no sign of systolic arrest induced by the digitalis. When the calcium was absent some change took place enabling calcium on its reintroduction to send the heart into systole. The facts leave no doubt, I think, that the action of digitalis in increasing the response of the heart to calcium is antagonized by calcium itself. The antagonism is mutual. The perfusion of the solution of high calcium content, such as was used above, for a given period of time rendered the heart much less responsive to calcium when digitalis was absent than when digitalis was present. The phenomenon of a substance assisting calcium in one action and antagonizing it by another is far from rare; in fact, it is the usual thing. Elsewhere I have given other examples of it (8, 9.)

Some other Effects of the Drug.

In the course of an investigation into the action of strophanthin, Clark (16) gives some evidence that acidosis was a factor in determining the cessation of the continued systolic state induced by that drug. Acidosis, as I have shown elsewhere, induces a cardiac state in which the heart becomes less responsive to calcium, so that the diminished amount of perfusion through the continuously contracted heart may assist dilatation through favouring the production of acid in the muscle in consequence of the diminished supply of oxygen. But it should only be regarded as *assisting* the process. The disturbance induced by digitalis is a self-limited one, and tends to subside once the digitalis has been removed from the perfusing solution. Its subsidence cannot easily be followed in the contracted heart, but if measures be taken to induce relaxation by altering the composition of the perfusing fluid, then the subsidence of the change can be followed as changes in the amplitude of the contraction of the beating heart, and presumably without the factor of inefficient oxidation.

When comparing digitalis with barium, the length of time taken in the cycle of events leading up to the assumption of the systolic state by the heart on adding digitalis to the perfusing solution, and the subsequent return to that of apparently

normal beating on removal of the digitalis, is of some interest. The time taken with digitalis varied between two and four hours.

The actions of the drug dealt with above are presumably those on which its therapeutic action depends. The preparation of digitalis used by me had another action on the heart, the general character of which is best brought out, perhaps, by comparison with the action of some other substances.

It is possible to experiment on a heart with such substances as alcohol, potassium, and adrenin, say, over long periods of time, e. g. eight hours, and at the end of that time that heart will only be found to differ quantitatively from the fresh organ. But once a heart had been made the subject of an experiment with the digitalis preparation used, the effects of that one experiment never seemed to leave it. Left to itself, as it were, that heart went on beating steadily—once such beating had been resumed after the systolic arrest—just like any other heart that had not been treated with the drug. But on attempting to utilize it for other experiments some form of anomalous behaviour was obtained. The experiments adequate to ascertain the nature of the change were not performed. It is sufficient, perhaps, to point out that the change was there, and that the change was observed so long as six hours after the digitalis had been removed from the perfusing solution. Its existence, perhaps, gives evidence for the view that digitalis can alter the chemical composition of cardiac muscle, but at the same time it should be noticed that the presumably therapeutic action of digitalis appears entirely distinct from this change.

The Toxicity of Barium Salts and the Barium Systole.

The term toxic must have a different significance to the observer working on the perfused heart from that which it has to one working on the intact organism. If, for example, there be introduced into the blood of a living animal a substance capable of stopping the heart in systole and in sufficient strength so to do, the experiment practically ends with that stoppage. But if the experiment be done on the perfused heart it may be possible to wash away the modifying substance and the heart begin to beat again.

In my experiments the perfused heart exhibited in marked degree a capacity for resuming function after treatment with barium. Thus, a single heart was treated as follows with

0·5 per cent. barium chloride 6 times
0·3 „   „   „   „   3 „
1·0 „   „   „   „   4 „
1·5 „   „   „   „   3 „
0·3 „   „   „   „   3 „
0·5 „   „   „   „   12 „

in the order named. The work was spread over a period of some nine hours. The final perfusion of the last series is shown in Fig. 3.

The heart went into systolic arrest on each of the occasions mentioned above. The mode of reaction was also typically a 'surface' effect. Directly after the barium containing solution reached the heart, systolic arrest came on ; and directly the same solution minus the barium was perfused, the heart relaxed again. The interval elapsing between the commencement of the systolic arrest and subsequent relaxation therefrom depended largely on the quickness of the operator in making the necessary change of solutions and the delay imposed by the apparatus. That is to say, keeping the barium as the only variable in the perfusing solution, the duration of systolic standstill lies within certain limits of the control of the operator. Nor, as will be seen in the figure above, does any continuation of the action of the barium conduce to any prolongation of the systolic state subsequent to the removal of the element. After twenty minutes' exposure to its action, relaxation after removal of the barium is not appreciably slower than after a two-minute one. Whatever the change may be taking place in the heart during systolic arrest induced by barium, that change does not persist as does the one induced by digitalis after removal from the perfusing solution of the substance originally causing its appearance.

The Antagonism by Calcium of the Barium Contraction.

Brunton and Cash (3) drew attention to an antagonism between barium and calcium. Ringer and Sainsbury (24) showed that an increase in the calcium content of a tonus-producing barium solution was followed by a decrease of tonus. Overton (21) also found an antagonism. The experiment below amplifies this result.

A physiologically balanced solution had 0·1 per cent. of barium chloride added to it and was then perfused. On varying its calcium content the following results were obtained :

Calcium content.			Amount of Tonus.
0·015	per cent. $CaCl_2$		Half
0·010	,,	,,	,,	Two-thirds
0·0025	,,	,,	,,	Complete
0·025	,,	,,	,,	One-fourth
0·005	,,	,,	,,	Complete
0·025	,,	,,	,,	One-fourth
0·005	,,	,,	,,	Complete
0·100	,,	,,	,,	Relaxed
0·005	,,	,,	,,	Complete

By half-tonus is meant that the rise of tonus reached a level about one-half that of the amplitude of the previous spontaneous contraction. One limit of the antagonism is reached when the solution does not contain calcium, and under those circumstances, as shown by Ringer and Sainsbury, a trace of barium suffices to induce marked tonus.

In explanation of this antagonism Ringer and Sainsbury suggested that the two substances attack a common structure and, in accordance with the law of mass action, produce effects in accordance with their relative concentrations, a suggestion with which one would only agree.

The amplification of the work of Ringer and Sainsbury given above, however, shows in marked degree the dissimilarity between the systolic state induced by digitalis and that induced by barium, an increase in the calcium content of the solution increasing the effect in the one instance and decreasing it in the other.

The State of the Heart induced by Barium.

When the response of a heart to calcium was examined before and after treatment with barium and in absence of barium from the perfusing solution it was found that barium salts left the heart in a state of decreased responsiveness to calcium as compared with what it had been before. The state of the heart induced by barium is thus the opposite of that induced by digitalis. Hence it should be possible to use digitalis as an antidote to barium. It can be so used, and an example of its use is given in Fig. 4 A.

The illustration gives, I think, the clearest evidence against the view of the similarity of the actions of the two drugs. The heart was perfused with a solution recommended by Ringer, its calcium content being that of saturation with the dibasic phosphate. Barium chloride (0·3 per cent.) was added to this, and the mixture perfused for some considerable time as shown. The tonus induced by the barium subsided on its removal from the perfusing solution, but the amplitude of the beats after that treatment was about two-thirds that existing before. The addition of the digitalis preparation to the perfusing solution was immediately followed by recovery of the heart, and the improvement persisted during a further period of two hours when the experiment was repeated.

An examination of the records above shows that the tonus induced by barium has a tendency to subside. This is, in part at any rate, the result of the decreased responsiveness of the heart to calcium induced by the barium, for the appropriate introduction of a drug increasing the response of the heart to calcium was followed by a restoration of the barium tonus. Adrenin was the drug chiefly used in these experiments. Digitalis had a similar effect. But it is on the former that reliance is chiefly to be placed, because as used in those experiments it has never been found to have such a marked action in increasing the tonus-producing power of calcium, and calcium was, of course, present in the solution in addition to the barium.

The inability of barium to maintain cardiac activity for other than a short time, as discovered by Ringer and Sainsbury, is also in part due to a gradual loss of response to the drug. Adrenin antagonizes this change, and the addition of a trace of adrenin to a solution containing barium enables the heart easily

to double its period of visible activity perfused with that solution.   Digitalis has a similar action in prolonging activity.

Some Circumstances influencing the Action of Barium.

The remarks made in the last paragraph lead to another point which is possibly of some importance, namely, that a given concentration of barium added to a solution of constant composition does not produce a constant amount of effect on the heart.   It varies according to the state of the heart.   The more responsive the heart is to calcium the more responsive it is to barium.

Thus the action of barium in producing tonus is reinforced by alkalinity, digitalis, adrenin, strophanthin, each of which has the common factor of increasing the response of the heart to calcium.   It may be noticed that the drugs assisting the action of barium assist also the heart to recover from the effects of barium.

The Replacement of Calcium by Barium.

This was examined by Ringer and Sainsbury (24).   To their work might be added the fact that barium salts can partially replace calcium salts functionally in regard to their necessity for the production of a 'contraction effect' by potassium (5, 7).

Another Action of Barium.

Overton (21) showed some time ago that calcium salts poisoned muscle by combining with phosphates.   Considering its close chemical similarity with calcium it is not unreasonable that barium may have some similar action.

The problem was attacked during the course of the prolonged experiments mentioned in an earlier section.   The damage done by a single experiment may not be adequate for its detection, but by making a large number of experiments on a single heart, it may be possible to obtain, as it were, a summation of damage.

The experiments showed that adrenin, digitalis, &c., had limitations in regard to antagonizing the action of barium.   Thus digitalis acted excellently as shown in Fig. 4 A, but on repeating the experiment on that same heart the effect was by no means so good especially, as regards the power of conduction.

The beneficial influence of the dibasic phosphate of potassium on hearts treated with barium is shown incidentally in Fig. 3.   The heart from which this tracing was obtained was the same as that from which Figs. 2 A, 2 B, 2 C, and 2 D elsewhere (4) were also obtained.   An interval of some seven hours elapsed between the periods of activity shown in Figs. 2 A elsewhere (4) and 3

after which traces of barium were employed to reduce the heart to the condition shown in Fig. 2 D elsewhere (4). Treatment with the dibasic phosphate of potassium was employed at intervals during the perfusion of barium salts mentioned in connexion with Fig. 3, and comparison between Figs. 2 A elsewhere (4) and 3 shows that the treatment had some degree of efficacy. Further evidence on this point is given in Figs. 5 A, 5 B, and 5 C.

In those figures illustrations are given of the beats of a heart when beating on its own blood before being subjected to experiment with barium, and of the beats of the same heart after some eight hours' exposure to barium in the manner mentioned in Fig. 3. The critic has probably observed in connexion with that figure that a 5 per cent. solution of the dibasic phosphate of potassium was used, a fact that raises several possibilities in regard to interpretation. The further facts that a saturated solution of the dibasic phosphate of sodium (about 3 per cent.) and a 5 per cent. solution of the chloride of potassium, while they gave results in the same direction, did not do so to the same degree, brings the possibilities down to what seems the improbable, namely, that there is something peculiar in this action of the dibasic phosphate of potassium. Yet I would submit there is a good deal in favour of the result, and give another diagram as further evidence. (See Fig. 6.)

The heart from which that tracing was taken had been poisoned by calcium, that is to say, it had been perfused for some time with a Ringer's solution containing 0·025 per cent. of calcium chloride.

At the extreme left of the tracing there was substituted for this solution a similar one, except that its calcium was added by saturating the solution with the dibasic phosphate of that element. The amount of calcium so introduced is about comparable with 0·01 per cent. $CaCl_2$. The beats of the heart immediately fell away and now became very small. The heart was next treated with a saturated solution of the dibasic phosphate of sodium, but without any improvement.

The heart was next treated with a 5 per cent. solution of the dibasic phosphate of potassium, and following its removal the beats of the heart became greater on the solution of lower calcium content than they had been previously on the solution containing greater amounts of calcium. But thereafter they fell away again until their amplitude was as small as they had been previous to the use of the potassium salt. A second treatment with the potassium salt was followed by an even greater improvement in the amplitude of the contractions than was the case with the first one, but again succeeded by a failure. But on this second occasion—acting on the hypothesis that the improvement observed was the result of ' loading ' the muscle with the dibasic phosphate of potassium and that the failure succeeding was due to the salt ' breaking away '—some of the dibasic phosphate was added to the perfusing solution with a view to hindering this loss, with the result that the improvement originally obtained was restored and maintained. Finally, return was made to the original modification of Ringer's solution, and it will be observed that as a result of the apparently

rigorous treatment to which the heart had been subjected, conduction, contraction, and rhythm had all been improved.

Results of the type shown above have been regularly obtained by me when sought for. I have not obtained the like by using potassium chloride. The results, however, give what is, I think, good evidence for a serious consideration of the possibility that loss of phosphates may occasionally be a factor in determining cardiac failure.

Incidentally, it may be pointed out that evidence given elsewhere indicates an antagonism between phosphates and chlorides.

Concluding Remarks.

In a former paper (4) I used some of the results given here on digitalis to show that clinical cardiac failure was the result of alterations in the relations between the heart and its normal perfusing solution, brought about either by changes in the heart itself or in its perfusing solution, or by both factors. It will be easily seen from the experiments above that barium would be unsuitable in such cases. If the 'state' of the heart, &c., has been depressed so that its response to calcium is inadequate for the proper maintenance of the circulation, the use of barium in such a case, while giving a temporary fillip to the heart, would leave its 'state' worse than before. For it will be remembered that whenever the 'state' of the heart was examined before and after treatment with barium, it was found that that treatment decreased the response of the organ to calcium. And in those cases where failure was possibly the result of an actual decrease in the calcium content of the perfusing solution, barium stands condemned by the experiments of Ringer and Sainsbury showing it to be an inadequate physiological substitute for calcium. The key-note to the understanding of the action of barium is the realization that it acts as an imperfect substitute for calcium, so that if it be introduced into the organism it will perform inadequately the functions already being carried on by calcium. And whatever effect is got from barium will be obtained in great part, if not wholly, at the expense of the calcium already present. The calcium and barium fight each other to determine which shall do the work. They are primarily antagonists rather than synergists. The experimental reputation of barium as a cardiac stimulant appears to depend on a lack of demarcation between the amount of the substance adequate to maintain spontaneous contractions and the amount that induces marked tonus. The two effects overlap when barium is used, whereas when calcium is employed they are easily separated.

This separation is still present when digitalis is used to increase the working efficiency of calcium. In this case we lubricate the cardiac machinery, as it were, the actual parts remaining on the whole the same as before. And it is upon this lubricating action of the drug that its therapeutic action depends.

The antagonism between calcium and digitalis serves to illustrate certain important principles in regard to the flexibility of the cardiac mechanism, viz.

that the flexibility or ease of reaction tends to vary indirectly with the calcium content of the perfusing solution. By varying that calcium content so it becomes possible to impose upon the heart a temperament whereby it reacts easily or with difficulty to a given dose of drug. I have found this to be the case with all drugs with which I have experimented that were capable of influencing the cardiac reserve.

According to the temperament of the heart so the effects produced by a given dose of drug may also differ, though a large series of experiments may serve to connect as different phases of a single event. For example, if an observer had made the assumption that the solution I used above to demonstrate the antagonism between calcium and digitalis was of the proper composition to perfuse a heart with, he might well think of the presence of peculiar and imponderable substances in the blood and their absence from his perfusing solution as accounting for the differences in behaviour of the heart when subjected to the influence of a given dose of drug presented to it in the two different solutions. Yet the solution used there, according to my own experiments, did not contain a proportion of calcium greater than the ordinary Ringer's solution, or serum, has over blood. There is an enormous difference between the temperament of a heart beating on an animal's own blood and of that same heart perfused with Ringer's solution, as to which some evidence is given elsewhere (4, 14). A difference in calcium tension is an important factor in determining these differences of behaviour. When the heart beats on Ringer's solution it beats on a solution in which the calcium does its work on its own, so to speak ; the calcium tension is high. When the heart beats on blood it beats on a solution containing calcium lubricants such as adrenin or pituitary extract; the calcium tension is low.

The low calcium tension of blood is possibly an important factor in enabling the organism to respond easily and quickly to changes in the reaction of that perfusing fluid. And for its ability to do its work in presence of small amounts of calcium the normal heart is dependent in great measure, if not entirely, upon the secretions of certain of the ductless glands. For example, traces of adrenin enable the heart to maintain activity over long periods of time in presence of such amounts of calcium as would otherwise be quite inadequate for the purpose (10).

To speak of the ductless glands and calcium recalls the work and views of Blair Bell (2). The principles laid down above throw fresh light on and enable us to modify some of his views. Thus suppose the internal secretion of the thyroid has a tendency to cause excretion of calcium (1). Over-production of thyroid secretion by reducing the calcium content of the blood, though not to the point of failure, would render the individual more easily reacting than normal, while an increase in the calcium concentration of the blood would produce a slowly reacting individual. The cretin can be regarded as a creature held in the bonds of calcium. And remembering that barium is a depilatory, it does not seem altogether wrong to believe that an excess of calcium in the body

might lead to loss of hair, for we also know of a tendency for that symptom to accompany calcification of arteries.

There is not, however, much immediate connexion between the two conditions with a common symptom. There are, however, two factors in the excitation process, and if, as suggested, thyroid secretion modifies one of them, the perfusing solution, defects arising therefrom can be overcome in part by attending to the 'state' of the organs just as one can use digitalis in similar circumstances for cardiac cases. Other internal secretions, e. g. the pituitary and adrenals, influence that state, and it may be that the pituitary hypertrophy observed in certain cases of thyroid insufficiency is the result of that gland having increased work thrown upon it to maintain a 'state' of the organs appropriate to the change in their perfusing solution, rather than its provision of a substitute for the missing secretion. On the other hand, in old age presumably all glands fail, with the result that perfusing solution and perfused organs undergo change without the one tending to compensate for the other.

To some extent calcium must be regarded as the *deus ex machina* of the body. It is important to realize that any particular heart beat represents a reaction of the heart to the calcium of its perfusing solution. When the hearts works inadequately or ceases beating it does so because the appropriate combination between the two factors no longer exists. But calcium, the 'adequate stimulus' of the heart, leaves behind a refractory state, and the problem of maintaining cardiac activity is primarily bound up with a complete reversal of that state. The more the work is done by calcium on its own, the less complete is the reversal. Perfused with Ringer's solution a heart grows 'old' and refractory in a few hours. The intact organism protects itself from, and makes use of, calcium by its ductless glands. They greatly enhance the exciting properties of calcium and so make possible its employment in smaller amounts, and they assist the reversal of the refractory state it leaves behind.

Summary and Conclusion.

1. The heart reacts in two chief ways to drugs, &c. In the one case the reaction comes on apparently immediately after the drug reaches the heart, and passes off equally quickly on removal of the drug from the perfusing solution. In the other the change usually shows a distinct time factor in its development and especially in its subsidence. This second type of change persists for some time after removal from the perfusing solution of the drug originally giving rise to it, and is to be regarded as a 'state' of the heart.

2. The cardiac mechanism is made up of two factors : the actual working parts and the accessories. A suggestion is given as to the nature of the working parts and their mode of interaction. It is also suggested that evolution has determined an optimum power of intraction with each other of the parts normally present.

3. Digitalis acts as an accessory to the normal mechanism. It enables one element of that mechanism, calcium, to perform more work in certain directions than would otherwise be the case. The therapeutic effect of the drug is dependent upon its induction in the heart of a ' state ' in which that organ becomes more responsive to certain actions of calcium. The change induced by digitalis is a self-limited one. It persists immediately after removal of the drug from the perfusing solution and then slowly subsides.

4. Barium acts as an imperfect substitute for an element of the normal machinery. When barium and calcium are present in mixtures the two elements attack common structures and produce their effects in accordance with the law of mass action (Ringer). Arguing from the results obtained with digitalis, cardiac insufficiency is due to alterations in the normal relations subsisting between the heart and the calcium of its perfusing solution (Burridge). The use of barium is thus contra-indicated in such conditions, for in employing it we should be using a substitute, imperfect even under normal conditions, to carry on the functions of an element at a time when that element is unable to do its own work properly. Moreover, whatever action barium produces is obtained at the expense of calcium already present.

5. The systolic condition induced by barium comes and goes respectively with addition to, or removal from, the solution of the element. This barium contraction may be produced many times—thirty was an actual number—in the same heart. In marked contrast with this the systolic condition induced by digitalis takes some time to come on, and a considerable time to pass off on removal of the digitalis from the perfusing solution.

6. Barium induces a ' state ' of the heart in which that organ has a decreased responsiveness to calcium. The ' state ' of the heart induced by barium is thus the opposite to that induced by digitalis, and it is shown that digitalis can act as an antidote to this damaging action of barium.

7. An antagonism exists between calcium and digitalis in regard to the ' states ' they induce in the heart.

8. It is shown that the temperament of the heart or its flexibility of reaction to a given dose of drug tends to change with the calcium content of the perfusing solution. Some general deductions are drawn from these experimental facts.

9. Some evidence is given that an inadequate supply of phosphates may determine a condition of cardiac insufficiency.

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DESCRIPTION OF FIGURES.

PLATE 18, FIG. 1. S ... = single induced shocks used to evoke contractions.
Between the marks + and ↑ the heart was faradized.
The illustration shows fusion of contractions approximating to tetanus, and 'superposition of twitches' in a heart treated with digitalis.

FIG. 2. A. 0·15 $CaCl_2$, 0·001 D = perfusion of solution containing 0·15 per cent. $CaCl_2$, 0·6 per cent. NaCl, 0·03 per cent. KCl, 0·01 per cent. $NaHCO_3$, and 0·001 per cent. digitoxin.
B and C show beats 20 and 40 minutes after experiment was begun.
D. At 'No Ca' the calcium was removed from the perfusing solution.
At 0·15 $CaCl_2$ the calcium was reintroduced.

PLATE 19, FIG. 3. R = perfusion of solution containing 0·6 per cent. NaCl, 0·025 per cent. $CaCl_2$, 0·03 per cent. KCl, 0·01 per cent. $NaHCO_3$.
0·5 $BaCl_2$ R = 0·5 per cent. $BaCl_2$ added to the above.
5 per cent. K_2P = perfusion of 5 per cent. K_2HPO_4 in 0·6 NaCl, followed immediately by solution 'R' above.
B = movement of recording apparatus apart from cardiac activity.

FIG. 4 A. CaHP = perfusion of solution containing 0·6 per cent. NaCl, 0·03 per cent. KCl, 0·01 per cent. $NaHCO_3$, and saturated with the dibasic phosphate of calcium.
0·3 $BaCl_2$. CaHP = addition of 0·3 per cent. $BaCl_2$ to above.
0·001 D, CaHP = addition of 0·001 per cent. digitoxin to 'CaHP'.

PLATE 20, FIG. 4 B. S ... = contractions artificially evoked by single induction shocks.
Sp. = spontaneous contraction.
Both figures traced by the same heart, ⦉ B being obtained 2 hours after ⦉ A. The heart was still under the influence of the digitalis, and the barium contraction was modified by this.

FIG. 5 A. Beats of a heart circulating its own blood at 11 a.m.

FIG. 5 B. Beats of same heart at 7.45 p.m.

PLATE 21, FIG. 5 C. Beats of same heart at 7.30 p.m., just after treatment with dibasic phosphate of potash.
This heart was treated with barium in a manner comparable with that mentioned in connexion with Fig. 3.

FIG. 6. At the extreme left of tracing the heart was perfused with a 'Ringer' containing 0·025 per cent. $CaCl_2$ (R), which at 'CaHP' was replaced by one saturated with the dibasic phosphate of calcium.
3 per cent. Na_2P = perfusion of a saturated solution of the dibasic phosphate of sodium followed immediately by the 'CaHP' solution.
5 per cent. K_2P = perfusion of 5 per cent. K_2HPO in 0·6 per cent. NaCl, followed immediately by CaHP.
CaHP 0·035 K_2P = addition of 0·035 per cent. K_2HPO_4 to the CaHP solution.
P. V. = excursions of lever due to manipulation, not to beats of the heart.
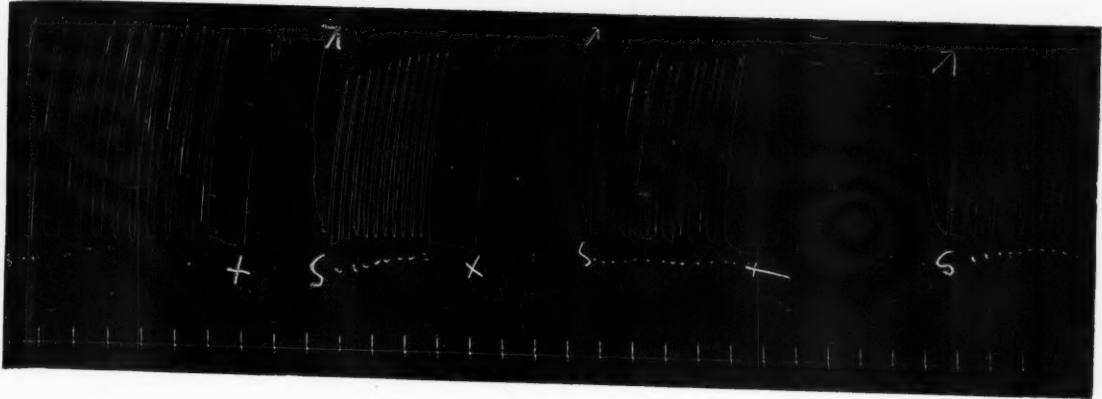
FIG. 1
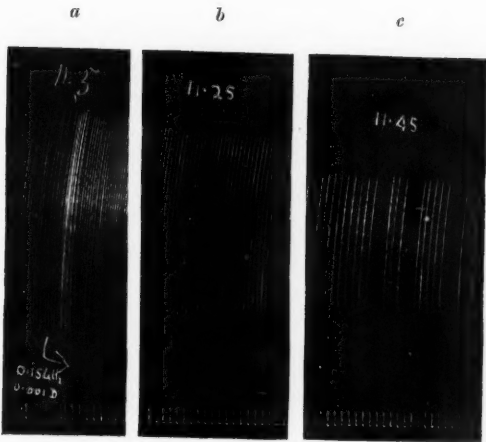
FIG. 2

FIG. 2 d
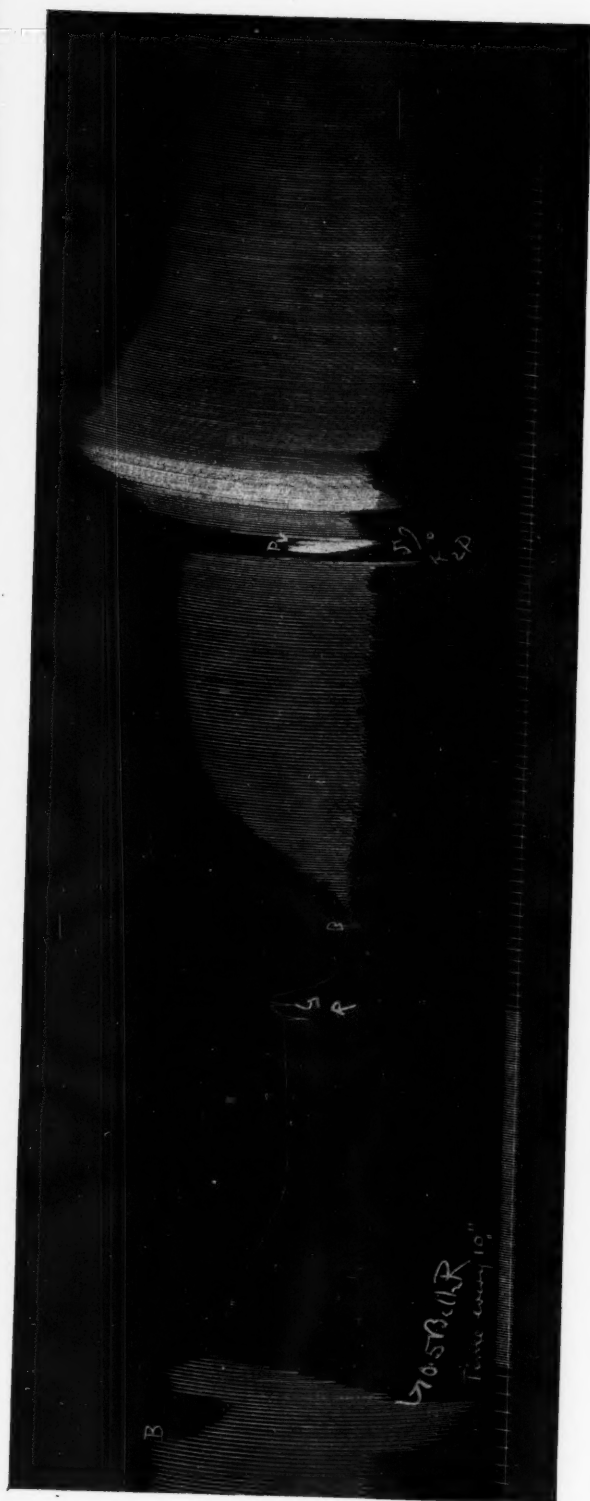
FIG. 3

FIG. 4 a

FIG. 4 b
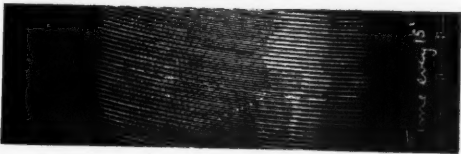
FIG. 5 b

FIG. 5 a

Fig. 5 c
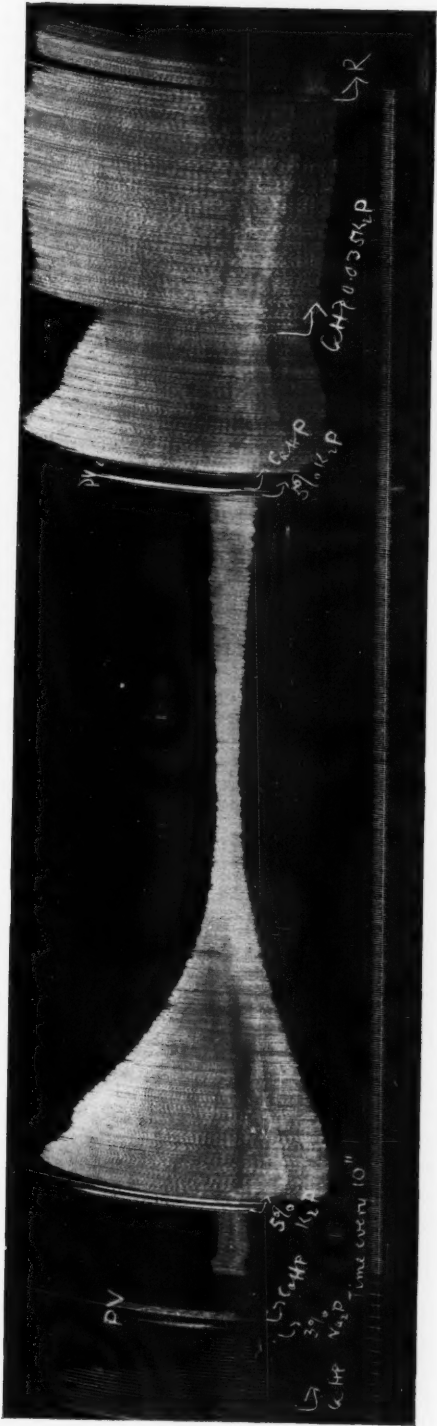
Fig. 6

THROMBO-ANGIITIS OBLITERANS

(NON-SYPHILITIC ARTERITIS OBLITERANS OF HEBREWS)

By F. PARKES WEBER

(From the German Hospital, London)

With Plates 22 and 23

I SHALL here endeavour to point out the chief features of the type of chronic arteritis obliterans which in Germany, England, and America has been chiefly or almost exclusively observed in male Jews between 30 and 52 years of age who have emigrated from Russia (especially Russian Poland), Roumania, &c. Thrombosis in the arteries supplying the affected parts (especially one or both feet) is such a true characteristic of the disease that I prefer Leo Buerger's name for it, 'Thrombo-angiitis obliterans'. Syphilis apparently plays no essential part in the aetiology of such cases, and the real cause of the vascular disease remains unknown, though tobacco-smoking may be suspected of being a contributory factor (see further on). Most of the patients have been free cigarette-smokers, and many of them have been employed in cigarette factories, where they could obtain cigarettes without paying for them. The characteristic symptoms of the disease are : (1) Redness or cyanosis of the foot when it is allowed to rest in a dependent position; (2) pallor of the foot on movement of the ankle-joint; (3) intermittent claudication, with feeling of cramp or pain in the muscles of the calf or instep on walking for a few minutes (Walton and Paul have termed this 'angina cruris' when, as in most cases, one of the lower extremities is the part affected); and (4) absence of pulsation in the arteries of the foot, notably in the dorsalis pedis artery.

In the case of a man, Marks M., aged 50 years, now under my care, the disease is of twelve years' duration, and on account of the typical nature of the symptoms, the very chronic course, and the periods of prolonged quiescence with remission or absence of pain, I have shown the patient on several occasions before the Clin. Sect. Roy. Soc. Med. Lond.[1] Both lower extremities are affected, but amputation has been hitherto avoided, although the patient has passed through periods of very painful ischaemic ulceration when gangrene appeared imminent. The channel of the radial artery at the right wrist has

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[1] i. 1. 1907–8, 44; iii. 1. 1909–10, 97; vi. 1. 1912–13, 72. See the *Proceedings* of those meetings, and likewise the accounts in the *Lancet*, Lond., 1908, i. 152, and 1913, i. 169.

recently become obliterated, but as yet there is no obvious trophic or motor disturbance in either hand—no pallor, abnormal redness, cyanosis, or muscular atrophy—excepting occasional sensation of coldness in the right thumb.

This case is at present (February, 1916), and has been off and on in 1914 and 1915, and was for some time in 1909 and 1910, complicated by red tender subcutaneous swellings due to multiple foci of superficial phlebitis of the lower extremities.   In this respect it resembles several other recorded cases, especially those described by Leo Buerger under the title 'Thrombo-angiitis obliterans'. In the amputated leg from a similar case (Solomon A., 1904) I found in one of the sections of the affected vessels that both the artery and one of the veins accompanying it were occluded by organizing thrombi—a fact which shows that the venae comites of the arteries may be likewise affected, and may be affected when the superficial veins are apparently unaffected.   I shall especially refer to this patient's case (Solomon A.) further on, and likewise to the case of a patient, Moritz K., in whom one of the venae comites of the anterior tibial artery was thrombosed.   In a paper on the subject in 1909 Leo Buerger summed up: 'The disease thrombo-angiitis obliterans is often associated with thrombo-phlebitis of superficial veins of the arms and legs.   Certain peculiar cutaneous nodosities are characteristic manifestations in many of the cases.   The disease of the super-ficial veins may be subsidiary, or it may dominate the clinical picture. . . . In the presence of migrating phlebitis or cutaneous nodosities we should carefully search for evidences of thrombo-angiitis obliterans in the form of pulseless vessels. . . . Migrating thrombo-phlebitis may give no symptoms, the signs referable to deep vessels being of most importance. . . . The morbid process resulting in the production of cutaneous nodosities and thrombosed superficial veins is independent of varicosities, of infections, or of trophic disorders in the territory which the veins drain.'[2]

In the case of Marks M., the disease has been rendered more severe by the occasional occurrence of chronic 'ischaemic' ulcers.   Such 'ischaemic' ulcers, when they occur in this class of cases, give rise to severe local pain and tender-ness, which keep the patient awake at night, like the pains of commencing dry gangrene of a limb; and, unfortunately, unlike the typical cramp-like muscular pains of the intermittent claudication, they cannot be avoided by keeping the muscles at rest, though they necessitate prolonged confinement to bed and the use of opiates, such as pantopon.   In this class of cases nature endeavours to establish a *capillary* collateral circulation in default of sufficient *arterial* collateral circulation, and that accounts for the hyperaemia and tur-gidity of the affected foot when it is allowed to hang down, a condition which has been confused with 'erythromelalgia' of nervous origin.   This explains why dilating the blood-capillaries in the foot by the temporary application of negative pressure (apparatus after Professor Bier), or by the local application

[2] Leo Buerger, 'The Association of Migrating Thrombo-phlebitis with Thrombo-angiitis obliterans', *Internat. Clinics*, Philadelph., 1909, 19th Ser., iii. 84.

of warmth, or by allowing the foot to hang down, may temporarily in some cases ease the pain and ultimately increase the efficiency of the capillary circulation in the part.

In regard to treatment, besides prolonged rest in bed (which is absolutely necessary in the bad cases, especially when there is any ischaemic ulceration) and the application of various methods to induce hyperaemia (by means of apparatus for negative pressure after Professor Bier, and the local application of warmth), and possibly also the use of electrical methods, I think that prolonged courses of iodipin really may exert some beneficial—though not rapid—effect. As local applications to the ischaemic ulcers xeroform, calcium iodide ointment (5 per cent.), Scharlachrot ointment (8 per cent.), and an application containing balsam of Peru with a minute quantity of silver nitrate, seem to be useful.

In some cases the disease becomes quiescent, or is arrested for a considerable time, before the period of 'ischaemic ulcers' is reached, and then, although the intermittent claudication may persist, there is not the dreadful nocturnal pain of threatened gangrene. It is this pain, if not the commencement of actual gangrene or septic infection of the part, which is specially likely to call for amputation. The case of Marks M. shows that occasionally a patient may safely pass through the painful period and escape amputation for several years at least. The tendency nevertheless is for the disease to commence again to advance, or to attack another extremity, even after a period of prolonged quiescence associated with considerable improvement in the local circulatory conditions. Another case (Benjamin R., aged 44 years, a Russian Jew, at one time employed in a cigarette factory and afterwards a tobacconist on his own account), which I demonstrated at the Clin. Sect. Roy. Soc. Med. on February 14, 1913,[3] well illustrated the not uncommon long quiescence of the disease at a relatively early stage. For $4\frac{1}{2}$ years the patient had suffered from 'intermittent claudication' in the left lower extremity. The right lower extremity was affected to a lesser extent, and pulsation could not be made out in the dorsal artery of either foot.

I have had the opportunity of seeing a good many cases of the affection amongst the Jews (chiefly from Poland) of the East End of London. The patients are all males and apparently free from syphilis. In the patient Marks M., the blood-serum has been examined on various occasions and has always been found to give a negative Wassermann's reaction for syphilis. A negative Wassermann reaction was likewise obtained in other cases, to which I shall refer further on in this paper.

In some cases amputation was thought necessary, but in other cases the affection seemed to become quiescent. The more, however, one sees of this class of case the less one favours any drastic operative interference. In two cases

[3] See F. Parkes Weber, *Proc. Roy. Soc. Med.* (Clin. Sect.), Lond., 1909-10, iii. 1. 96, and 1912-13, vi. 1. 162.

(patients S. A. and J. M.[4]) in which both lower limbs were badly affected (amputation on both sides), the radial artery in one of the upper limbs (as in the patient Marks M.) was found to be pulseless or partially obstructed, though no definite circulatory or other symptoms had been as yet caused thereby.

In some cases the disease early takes an acute course and one or more of the toes (and possibly part of one or both feet besides) soon become gangrenous. In a patient, Abraham G., aged 45 years, a Russian Jew, at present (April, 1916) under the care of my colleague, Mr. A. Compton, at the German Hospital, the disease, which commenced five years ago (in 1911), has already extensively involved both feet and both hands. The Wassermann reaction is negative. Pulsation cannot be felt in either arteria dorsalis pedis and can scarcely be felt at either wrist. The left great toe recently became gangrenous, but operative interference has been confined to assisting nature in the separation of the necrosed part.

In regard to diagnosis, it must be remembered that the single symptom expressed by the term 'intermittent claudication', in one or both lower extremities, may undoubtedly occasionally occur in the apparent absence of any organic arterial disease sufficient to account for it. Apart from Déjerine's cases of 'intermittent spinal claudication',[5] in a few cases the intermittent claudication of the lower extremities has been supposed to be due only to angiospasm (H. Oppenheim,[6] H. Curschmann,[7] and others), and in a few other cases no satisfactory explanation of the symptom can be obtained (by ordinary clinical methods of examination). Oppenheim [8] has found intermittent claudication combined with neuroses or psychopathic conditions, and occurring in persons in whom the stigmata of degeneration—e. g. medullated nerve fibres in the retinae, malformed fingers, &c.—pointed to the congenital disposition, and he says that his experience has been confirmed by Goldflam, Higier, Idelsohn, and others. In this connexion it may be noted that a son of my patient Marks M. is a well-grown lad of 23 years, but since the age of 6 or 7 years he has suffered from frequently recurring attacks of headache and vomiting. He (the son) also has or had slight chronic enlargement of the spleen ; his blood-serum gives a negative Wassermann reaction for syphilis.

In the case of a Jewish tobacconist, Louis M., aged 36 years (from Russian Poland), whom I first saw in 1905, treatment for 'flat-foot' had been at first adopted.[9] The disease is not rarely first mistaken for flat-foot (which is certainly

[4] Both these cases are referred to further on in this paper.

[5] See Déjerine, *Presse médicale*, Paris, 1911, xix. 981, and Déjerine's earlier papers of 1906 and 1909 on the subject ; P. Sollier, *ibid.*, 1906, xiv. 677 ; F. F. D. Reckford, *Amer. Journ. Med. Sci.*, 1912, N. S., cxliv. 721 ; S. Gavazzeni, *La Clinica Med. Ital.*, Milano, 1907, xlvi. 165 ; and G. Poggio, *Gazzetta degli Ospedali*, Milano, 1908, xxix. 138.

[6] H. Oppenheim, *Text-book of Nervous Diseases*, English translation by A. Bruce, 1911, 587.

[7] H. Curschmann, *Münch. med. Woch.*, 1907, liv. ii. 2519.

[8] Oppenheim, *op. cit.*, 586.

[9] In the case of Joseph M. (not a relative of Louis M.), referred to further on, treatment for 'flat-foot' had also apparently at one time been adopted.

present in some cases), rheumatism, gout, or some kind of ' neuritis '. Sometimes the symptoms have been supposed to be connected with ingrowing toe-nail, and the first obvious gangrene may follow the operative removal of a toe-nail.

One feature in the case of Marks M. is perhaps worthy of special attention. In my account of 1907 [10] I described it in the following words : ' If the patient then forcibly flexed and extended the ankle-joint a few times the skin of the foot in less than a minute lost its congested look and became blanched and alabaster-like.' A somewhat similar blanching of the hands on movements was noted by Oehler in a case of ' intermittent dyskinesia of the arms ',[11] and Erb [12] has proposed to call the phenomenon in question ' Oehler's symptom '. I have likewise alluded to the symptom elsewhere,[13] and S. Goldflam, of Warsaw,[14] has specially directed attention to it. The symptom is, however, in some cases very little noticeable, or apparently absent. In some cases it may be rendered more definite by first immersing both the patient's feet in a hot foot-bath so as to produce a preliminary artificial hyperaemia.

Pathological Anatomy.

Transverse sections of the arteries show various stages of vascularized thrombus, often combined with more or less endarteritis obliterans. I think that the severe symptoms of the disease are practically always due to *actual thrombosis*. The microscopical appearances vary with the degree of the local disease and its chronicity. Much depends also on the position of the transverse section examined. In some positions the changes may be chiefly secondary to the blocking of the artery higher up. I reproduce here (Fig. 1, Plate 22) an illustration of the transverse section of the dorsalis pedis artery from a typical example of the disease described by Dr. E. Michels and myself in the *Brit. Med. Journ.* 1903, ii. 566. The patient, Solomon A. (aged 37 years in 1903), was a Jewish tailor in London who had emigrated from Russian Poland in 1897. He had been accustomed to smoke a considerable number of cigarettes daily, but there was absolutely no evidence of syphilis, alcoholism, renal disease, saturnism, ergotism, or premature senility. Partial gangrene of the big toe occurred in 1899 (in the *Brit. Med. Journ.* the date was given by mistake as 1900). In 1902 the right big toe became affected. Later in the same year absence of pulsation was noted in the left radial artery, though no cutaneous or muscular disorder was observed in connexion with it. The right foot was amputated in September, 1902.

Examination of the amputated right foot of Solomon A. Sections for

[10] *Proc. Roy. Soc. Med.* (Clin. Sect.), Lond., 1907-8, i. 1. 44.

[11] Oehler, *Deutsch. Arch. für Klin. Med.*, Leipz., 1908, xcii. 154.

[12] Erb, *Münch. med. Woch.*, 1910, lvii. i. 1181.

[13] F. Parkes Weber, *Proc. Roy. Soc. Med.* (Clin. Sect.), Lond., 1909-10, iii. i. 97 ; (Neurol. Sect.), 1907-8, i. ii. 50 and 102.

[14] See Goldflam's remarks on this subject in the *Münch. med. Woch.*, 1910, lvii. ii. 1747.

microscopical examination were cut from the following parts: (1) dorsalis pedis artery, near the site of amputation; (2) internal plantar artery; (3) extensor brevis digitorum and adductor pollicis muscles; (4) a piece of skin from the dorsum of the foot. The muscles and skin showed practically nothing abnormal, but the two arteries examined were found blocked. The lumen of the internal plantar artery was blocked by blood-clot, in which organization was commencing in the peripheral portions, that is, the portions adjoining the diseased and somewhat thickened intima. The elastic layer of the intima (the 'fenestrated membrane of Henle') could not be made out, and the layers of the muscular coat (tunica media) were separated by cellular infiltration. There was likewise a good deal of infiltration in the tunica adventitia and surrounding connective tissue. The lumen of the dorsalis pedis artery was occupied by newly-formed connective tissue, in which were many pigment granules (doubtless haemosiderin) and several small channels lined by endothelium, some of them occupied by red blood-corpuscles. The intima was thickened, and its elastic layer, which (unlike that of the internal plantar artery) remained distinct, formed a very wavy line, showing that the artery was not distended by the material blocking its lumen. The middle and external coats were practically normal, but in the neighbourhood was some cell infiltration around a minute arteriole (one of the vasa vasorum).

The question arises, Was the blocking of the dorsalis pedis artery the result of thrombosis with subsequent organization, or was it the result of proliferative endarteritis with subsequent vascularization of the proliferating intima? In the latter case one (or more) of the channels lined by endothelium might represent the remains of the original lumen. On the other hand, the presence of the pigment granules (haemosiderin?) points to there having been thrombosis with subsequent organization of the clot, the channels lined by endothelium being probably newly-formed blood-vessels in the organized thrombus. The bones of the foot were found to have undergone no atrophic process.

Later on, in the same patient (February 26, 1904), the right leg was removed by amputation just below the attachment of the patellar ligament. On naked-eye examination of the anterior and posterior tibial arteries in the amputated limb they were seen to be practically blocked throughout. Microscopical sections showed organizing thrombus and proliferating endarteritis. Two venae comites (one in each of two separate groups of vessels examined) were likewise occluded by organizing thrombus. The patient died somewhere on the continent of Europe, about November, 1907. I have a note that in December, 1904, his left radial artery was still pulseless at the wrist, but there was no trophic change to be made out in either hand, and in both hands the grasp was strong.

In the *Trans. Path. Soc. Lond.* 1905, lvi. 223, Dr. Michels and I described another case of the same disease with the microscopical findings. The patient, A. H., was a Roumanian Jewish cigarette-maker, aged 39 years. He formerly had enjoyed good health, but in 1888, at the age of 23 years, he commenced to have 'intermittent claudication' in the right lower extremity. At Riga, in 1889,

after more than a year of suffering, the right leg was amputated below the knee-joint. After that he remained well for a time, but in June, 1903, he began to complain of intermittent claudication in the left lower extremity, with pains similar to those he had had in the right leg. There was no history of alcohol or any venereal disease, but the patient had been accustomed to smoke a good many cigarettes daily. At the patient's repeated request Dr. Michels amputated the left leg below the knee on October 7, 1904. The popliteal artery was found to be completely blocked at the site of amputation. Microscopical transverse sections of the popliteal artery (see Fig. 2, Plate 23) showed its lumen obliterated by fairly dense connective tissue, containing a great number of newly-formed blood-vessels and a certain amount of pigment granules, doubtless derived from blood (haemosiderin), and probably indicating that that part of the connective tissue obliterating the arterial lumen was the result of organization of a thrombus. The elastic lamina of the internal coat was well preserved, and at some parts of the wall it was doubled. At some parts also there was a certain degree of proliferative endarteritis. The anterior tibial artery was occluded by con-nective tissue similar to that noticed in the popliteal artery, and almost certainly the result of organization of a thrombus. The elastic lamina was distinct and very wavy in outline. Transverse sections of the dorsal artery of the foot (Fig. 3) showed an extreme degree of endarteritis proliferans, so that its lumen was greatly contracted, but not completely occluded. Much of the thickened inner coat had been converted into connective tissue by a process of organization, with formation of new blood-vessels. The elastic lamina was deficient at one part.

In two other patients I have had an opportunity of microscopically examining diseased blood-vessels. Joseph M., a Polish or Russian Jewish tailor in London, was 52 years old when I first saw him in 1907. He was a cigarette-smoker like the other patients with the same disease. About 1904 he had commenced to suffer from pain in the sole of the left foot on walking, and about half a year later ' intermittent claudication' in that limb had become pronounced. In 1907 the end of the left foot was of a livid blue colour, and often felt cold. He had apparently been treated for ' flat-foot'. At that time there were no subjective symptoms of disease in the right foot, though no pulsation could be felt in the dorsalis pedis artery of either foot. In December, 1907, the left leg was amputated below the knee at another hospital in London. In January, 1910, there were obvious circulatory signs of the same disease in the right foot,[15] and there was a small deeply punched-out chronic ulcer, resembling a ' perforating ulcer ', of nine or ten weeks' duration, on the ' ball' (metatarso-phalangeal region) of the right great toe. I should here mention that there was no history of any venereal disease or of excessive indulgence in alcohol. The Wassermann reaction for syphilis was negative (November, 1911). In November, 1911, there was some dry gangrene of the right great toe, and there was likewise a little pyrexia, apparently from septic absorption. A previously existing ulcer had

[15] See F. Parkes Weber, *Trans. Med. Soc.*, Lond., 1910, xxxiii. 394.

become deeper.   On November 24, 1911, my colleague, Dr. E. Michels, amputated the right leg at the knee-joint.

In the popliteal artery of the amputated limb a patch of thickened arterial wall projected like a bolster into the lumen.   Below the division of the popliteal artery the main arterial circulation was almost entirely blocked.   The anterior tibial artery seemed to be closed at its commencement.   The posterior tibial artery was blocked after giving off the peroneal artery.   The peroneal artery was much narrowed.   All the arteries appeared small (hypoplastic) in relation to the patient's size.   Microscopical sections of the popliteal artery (close to its bifurcation), the anterior tibial artery, the posterior tibial artery, and the arteria dorsalis pedis showed obliterative changes, as from old organized thrombus, with more or less canalization and some hyaline-like degeneration in the muscular coats (at one spot in the anterior tibial artery there was some cholesterin débris). The lamina elastica could not be traced all round the arterial wall, except in the dorsal artery of the foot, in which latter vessel it was extremely wavy (signifying that the lumen was not distended) ; the muscular coat in the dorsal artery of the foot showed less decided degenerative changes than it did in the other vessels examined.

The amputation wound healed up slowly.   In July, 1911, the pulsation in the radial artery at the right wrist was already noted to be weaker than at the left wrist, and in March, 1916, the pulsation in the right radial artery was extremely deficient, though the patient did not complain of any symptoms in either upper extremity.   There was, however, a troublesome tenderness in the stump of the right lower limb, which likewise became flushed when in the dependent position.

In the other patient, Moritz K., aged 31 years, a Russian Jew, the right leg was amputated for commencing gangrene (1908) at about a hand's breadth below the knee.   The disease had commenced about two years previously, with pains in the right leg on walking, and there was the usual history of cigarette-smoking. Dr. E. Michels very kindly allowed me to study microscopic sections from the blood-vessels of the amputated limb, and told me that macroscopically the arteries had appeared to him to be rather hypoplastic.   The posterior tibial artery showed organized thrombus, containing pigment granules (haemosiderin ?).   The upper part of the posterior tibial artery showed no thrombosis, but much narrowing of the lumen from a kind of endarteritis obliterans.   The lumen of the lower part of the posterior tibial artery was likewise not obliterated ; about the small vessels (vasa vasorum) surrounding it there was considerable cell-infiltration.   One of the venae comites of the middle part of the anterior tibial artery was obliterated by organized thrombus [16] containing pigment granules (haemosiderin ?).

[6] In this connexion it may be noted that Leo Buerger (' Thrombo-angiitis obliterans ', *Amer. Journ. Med. Sci.*, 1908, N. S., cxxxvi. 567) thinks that the posterior tibial co-veins are often closed, while the anterior tibial veins are open.

Aetiology.

From the aetiological point of view in these cases I do not think that traumatism comes often into consideration. But in one case, a Russian Jewish tailor, A. S., aged 25 years, whom I showed at the Clin. Sect. Roy. Soc. Med. on March 12, 1915,[17] I drew attention to the occasional connexion of the disease with local injury. The exciting cause of the onset of the right foot symptoms in A. S. was a kind of 'frost-bite'; but he had already previously had disease in the left foot without 'frost-bite' of any kind being connected with it. The Wassermann reaction was negative. In another patient (1915), S. H., aged 37, a Jew who had been in South Africa, the diseased (left) foot had certainly been run over by a cab, but the patient had complained of pains long previously, and slight atrophy of the calf-muscles of the (left) leg had been recorded three months before the accident, when the patient was at a health resort for treatment. In a Jewish cap-peak-maker from Russian Poland, Abraham K., aged 52 years, ischaemic gangrene commenced in the right hand (1908) shortly after an accident in which he knocked his right thumb; but it was not quite clear that this case belonged to the class under consideration.

In regard to the question of aetiology, I may be permitted to refer to another recent case of mine, because it shows that the typical disease may develop in a Jew from Central Europe, though resident in England since early childhood. The patient in question, S. M., aged 38 years, a Jewish tailor in London (whom I showed at the Dermatol. Sect. Roy. Soc. Med. on May 20, 1915),[18] was, when only one year old, brought by his parents from Prague (Bohemia) to London, and had remained in England since then. The Wassermann reaction was negative. In another patient, L. K., aged $24\frac{3}{4}$ years, likewise a Jewish tailor in London, the history given was that he was a native of Moscow, but had been brought from Russia to London when only $2\frac{1}{2}$ years old. Two and a quarter years previously he felt a cramp-like pain in the calf-muscles of his right leg on coming home from work, and since then he had suffered from typical 'intermittent claudication' of that limb. The onset of the symptoms was therefore remarkably early in L. K.; he was only just over 22 years of age when they commenced. The constant working of a treadle (sewing-machine) may in his case possibly have acted as a determining factor.[19] For the last nine years he had smoked a good many cigarettes every day. His Wassermann reaction was negative.

[17] F. Parkes Weber, *Proc. Roy. Soc. Med.* (Clin. Sect.), Lond , 1914–15, viii. i. 49.

[18] See F. Parkes Weber, 'Spurious Erythromelalgia: Remarks on Non-Syphilitic Arteritis Obliterans in Jews', *Brit. Journ. Dermatol.*, Lond., 1915, xxvii. 197.

[19] See F. Parkes Weber, 'Intermittent Claudication of the Right Lower Extremity in a Young Man whose Business has been to work a Treadle Machine', *Proc. Roy. Soc. Med.* (Clin. Sect.), Lond., 1912–13, vi. i. 215.

Conclusions.

The affection occurs almost exclusively among adult Jewish males, of young or early middle age, especially those from the eastern portions of Central Europe. One of my patients was, however, only one year old, and another was only 2½ years old, when they migrated to England. The affection is not absolutely limited to the poorer classes; I have met with one case,[20] and know of another,[21] in which the patient was in very good financial circumstances. In nearly every case there is a history of habitual cigarette-smoking, and in some cases the patients, owing to being employed in cigarette factories, have been able to smoke large numbers of cigarettes daily without paying for them. It seems that there is nothing peculiar from the chemical point of view in the cigarettes which are smoked by this class of patients,[22] and it is extremely improbable that the cigarette-smoking is more than a contributory factor in inducing the disease. The essential cause of the disease still remains unknown. In some cases there appears to have been a certain degree of congenital hypoplasia, or deficient development, of the affected arteries. (See back for descriptions of the macroscopic and microscopic appearances of the diseased blood-vessels.) In the typical cases met with in London, evidence (by the history, Wassermann reaction, &c.) of acquired or inherited syphilis is remarkable for its almost invariable absence. The blood-pressure is seldom high, and there are seldom signs of general arteriosclerosis or of chronic interstitial nephritis. I have not included any glycosuric and diabetic cases amongst those referred to in the present paper. Usually one of the lower extremities is the site of the first symptoms, but the other lower limb is often attacked later on, and occasionally one or both upper extremities or another part of the body become involved.

The affection progresses by periods of exacerbation, alternating with long periods of remission. Surgical interference (amputations, which should not be performed too high up), when it becomes necessary, is chiefly called for owing to intolerable pain and insomnia during exacerbations associated with ischaemic ulceration, or to the occurrence of acute septic complications. Amputation seems, according to Leo Buerger's publications on the subject, to have been much more frequently resorted to amongst the sufferers at the Mount Sinai Hospital at New York than amongst those in London. In regard to the

[20] A merchant, aged 42 years (1911). Both lower extremities were affected. Pulsation was absent from the right radial artery, though nothing else abnormal was noticed in either upper extremity. The Wassermann reaction was negative. The first symptom of the disease was 'intermittent claudication', said to have commenced eight years previously.

[21] A cigarette-manufacturer, I think.

[22] In the case of a man, Moritz C., aged 42 years, whom I saw first in 1905, and who had typical symptoms of the disease in the right lower extremity, Dr. J. H. Ryffel kindly examined (1906) some of the patient's cigarettes for morphine, but with a negative result. The patient in question served behind the counter in a small grocery shop which he owned, but he sold cigarettes in addition to the grocery, and was consequently able to obtain them at very little cost.

avoidance of amputation, much depends on whether the patient has sufficient patience and powers of endurance to carry him over the periods of painful exacerbation of the disease. The affection is sometimes complicated by attacks of phlebitis and venous thrombosis (see back—the examples referred to), but these are generally recovered from without the patient's condition having been obviously rendered (permanently) worse.

'Intermittent claudication',[23] when it occurs in one or both lower extremities, is generally described as a cramp-like pain in the muscles of the calf or in the small muscles of the foot, induced by walking, but rapidly recovered from on resting, and then recurring at more or less regular intervals, if, after resting, the patient tries to walk again. This term, 'intermittent claudication', should not be regarded as synonymous with the disease under consideration; it is only a symptom of the disease, and likewise occasionally occurs as an important symptom in other diseases, such as syphilitic arteritis, and in conditions resulting from traumatism of arteries. Moreover, it plays no part in the symptomatology of very bad cases, i. e. when the patients are absolutely unable to get about at all.

The symptomatic term 'erythromelalgia', originally introduced by Weir Mitchell, has been employed for various conditions of vascular or nervous or trophoneurotic origin, including even some cases with cyanosis and swelling of extremities of only functional origin. Etymologically it is well adapted to be applied to the class of cases under consideration, meaning, as it does, *a painful condition of an extremity associated with redness (or cyanosis)*. But the cases under consideration are almost certainly not of the kind to which the term 'erythromelalgia' was originally applied. There are also objections to speaking of the disease as 'spurious erythromelalgia' or 'pseudo-erythromelalgia'. Personally, I think it would be best for the term 'erythromelalgia' to be employed only symptomatically, that is to say, as expressing the symptom-complex ('symptom-group' or 'syndrome') of pain in an extremity, associated with redness or cyanosis, especially when the limb is allowed to hang down, or is kept in a dependent position, favouring venous and capillary congestion.

In regard to diagnosis, I have alluded to the symptoms of the disease being at first occasionally supposed to be due to ingrowing toe-nail, flat-foot, rheumatism, gout, or some kind of 'neuritis'. The conditions symptomatically known as 'intermittent claudication' and 'erythromelalgia' may both of them

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[23] The French term, *claudication intermittente*, was first employed by H. Bouley, junior, in 1831, in regard to a rare arterial affection in horses, usually affecting one or both of the animal's hinder extremities. Under the name *claudication intermittente des extrémités*, Charcot, in 1858, described similar symptoms in man. *Intermittirendes Hinken* is simply the German translation of the French term. In 1898 Erb suggested the term *Dysbasia intermittens angiosclerotica*, and in 1902 Walton and Paul (America) proposed the term *Angina cruris*. For cases in which the upper extremities were affected, H. Determann (1905) employed the term *Dyskinesia intermittens*, and for analogous disorders in the intestines and abdominal viscera, N. Ortner (1903) introduced the term *Dyspragia intermittens*, and F. Perutz (1907) the term *Angina abdominis*.

sometimes occur in other diseases.   Conditions of one or both lower extremities resulting from arterial obstruction of other kinds (especially syphilitic cases) are those most likely to be confused with thrombo-angiitis obliterans.   Cases of Raynaud's syndrome and of sclerodactylia can seldom lead to such a mistake, though sclerodactylia of one or both feet does of course occasionally occur in adult Jewish males, of young or early middle age, and in some cases of sclerodactylia pulsation cannot be felt in any of the pedal arteries.[24]

[24] See F. Parkes Weber, 'Two Cases of Sclerodactylia', *Brit. Journ. Dermatol.*, Lond., 1915, xxvii. 113.

ADDITIONAL NOTE.

In regard to the possible contributory influence of cigarette-smoking in this disease, I wish to emphasize the fact that I have never come across an instance of the disease in a woman, nor yet in a man who was not, or had not been, a free cigarette-smoker.   Moreover, my observations and inquiries make it certain that the women of the Jewish families in the East End of London are practically all absolute abstainers from tobacco.   Smoking amongst these women is unknown and unheard of, though their men-folk are so notoriously fond of it.

F. P. W.
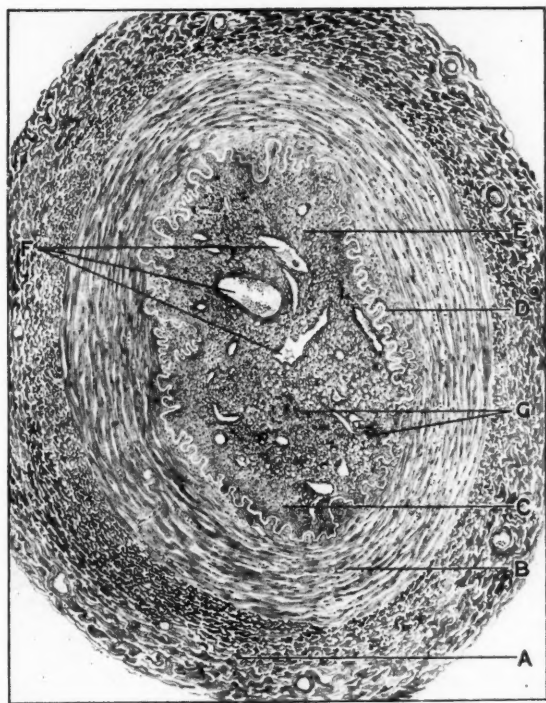
FIG. 1. Dorsalis pedis artery from case of Solomon A.   A, tunica adventitia; B, tunica media; c, tunica intima, irregularly thickened, separated from the tunica media by the wavy elastic lamina (D).   The space within the intima is filled with newly-formed connective tissue (E).   In this connective tissue are several channels (F) lined by endothelium, some of them containing blood, and scattered in its meshes are bright brown pigment granules, a special collection of which has been somewhat diagrammatically indicated in the drawing at G.
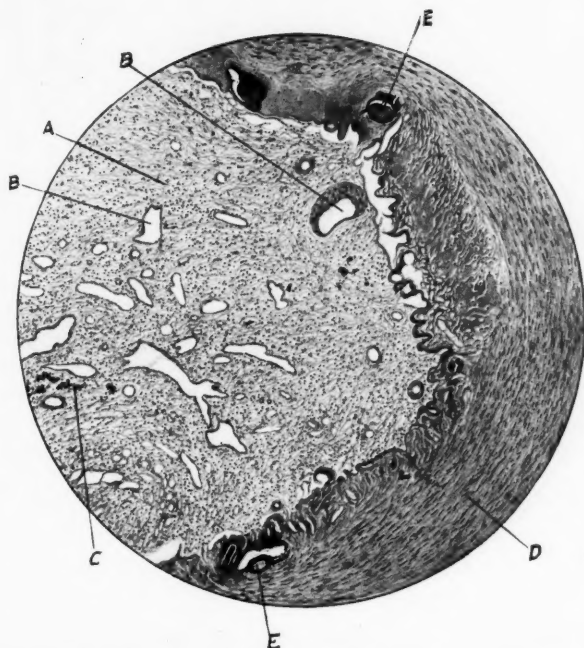
FIG. 2. Transverse section of part of the popliteal artery (magnified 60 times) from the case of A. H. The channel is obliterated by connective tissue (A). In this are many newly-formed blood-vessels (B), and in some parts groups of brown pigment granules, some of which are here represented diagrammatically in black (C). D = the middle coat. There are some small areas of calcification (E) just outside the elastic lamina, which is not very distinctly seen in the section illustrated.

FIG. 3. Transverse section of the dorsalis pedis artery (magnified 60 times) from the case of A. H. The lumen is contracted and nearly obliterated by proliferative endarteritis. The greatly thickened inner coat, bounded externally by the clearly defined wavy elastic lamina, consists chiefly of connective tissue containing many newly formed blood-vessels.

THE FOUR CARBON ATOM ACIDS OF DIABETIC URINE

By WILLIAM HOLDSWORTH HURTLEY

(From the Chemical Laboratory, St. Bartholomew's Hospital)

THE DISCOVERY OF β-HYDROXYBUTYRIC ACID.

THE presence of β-hydroxybutyric acid in diabetic urine was discovered by two very different methods. It was first discovered by E. Külz (1, 2). This author was desirous of determining the amount of urochloralic acid excreted by diabetics who had been given from 2·5 to 10 grm. of chloral. For this purpose the urine was fermented and the rotation of the fermented urine determined: the magnitude of the rotation obtained in some cases surprised Külz, and he concluded that it must be due to some other laevo-rotatory substance than urochloralic acid. He therefore repeated his experiments, omitting the chloral, and still obtained, in some cases, the high laevo-rotation. Haas (3) had observed the occurrence of a laevo-rotatory substance in normal urine, and Külz satisfied himself in the first place that this substance did occur in normal urine, and in the second place that his high laevo-rotation of the diabetic urine was not due to Haas's substance, nor to any other known laevo-rotatory compound such as albumin, peptone, albumose, leucine, tyrosin, amyl alcohol, and the like. To satisfy himself on the first point, he examined fifty normal urines and found Haas's substance present in all of them ; to satisfy himself on the second point he showed that the high laevo-rotation of the diabetic urine persisted after treatment with basic lead acetate and ammonia, a combination of substances which removes Haas's compound from urine, while all the other known laevo-rotatory substances were excluded by appropriate tests. Külz then proceeded to isolate and analyse his new compound and certain of its salts. The compound he describes as a colourless, transparent, odourless syrup which is not volatile in steam, gives no colour with ferric chloride, is oxidized to carbon dioxide, a volatile fatty acid, and acetone, by potassium dichromate and sulphuric acid, and forms a specially beautiful silver salt. Here are his analyses :

	Acid.		Silver Salt.	
	Found.	Theory.	Found.	Theory.
C	46·19	46·15	22·97	22·75
H	7·74	7·69	3·46	3·32
Ag			50·86	51·18

He determined the rotation of the pure silver salt in a saccharimeter.

Since the acid differed from the known oxybutyric acids in being optically active, he called his new acid pseudo-oxybutyric acid.

As to the occurrence of the acid in diabetes, Külz examined the urines of fifty-two patients suffering from this disease, and found it to be excreted in twenty-two instances. When a positive ferric chloride reaction was obtained, the urine which gave it always contained β-oxybutyric acid, and he found the acid on eight occasions when there was no positive ferric chloride reaction. In one of his cases he estimates the amount of the acid excreted in twenty-four hours by determining the rotation of the fermented urine and *assuming* that the specific rotation of the acid is only one-third that of glucose, and in this way he arrives at 226·5 grm. It is clear that he only guessed at the specific rotation of the acid and did not intend this to be taken as a real estimation of the acid. But Minkowski (4), Stadelmann (5), Magnus-Levy (6, 7), and von Noorden (8) have all quoted this as a real estimation. Magnus-Levy (6) recalculates it on the 'now better known constant'. The 'now better known constant' was Minkowski's (4) specific rotation of −20·6°, whereas Külz (9) had found −23·4°, the correct figure being −24·12°, as found later by Magnus-Levy (10) himself. Külz points to the well-known discrepancy which is often found between sugar estimations in diabetic urines, according as they are made by rotation or reduction, and explains it by his acid. Finally, he thinks it quite possible that his acid stands in a definite relation to the so-called acetonuria.

The other way in which β-hydroxybutyric acid was discovered was much more tortuous. Many workers, starting with Miquel (11) in 1851, had given strong mineral acids to animals and observed an increase in the amount of bases excreted : thus Miquel fed a dog on bread and water and then gave dilute sulphuric acid (1·2 grm. pure acid) on two days with the following result :

	No acid.		Acid.	
	Day 1.	Day 3.	Day 4.	Day 5.
Total solids	4·31	5·7	6·9	5·7
Salts	1·50	1·6	4·0	3·0
Reaction of ash	Alkaline	Alkaline	Weak acid	Alkaline

Gaethgens and Frey (12), who trained their dogs to pass their urine at definite times when let out of their cages, fed them on a definite diet, and gave the diluted acid by the gastric sound, found the quantity of fixed bases far from sufficient to neutralize the sulphuric acid excreted at the same time. Kurtz (13), in a paper not accessible to me, seems to have suspected that the excess of acid was neutralized, at all events in part, by ammonia.

E. Salkowski (14) discovered that different classes of animals react differently towards administered taurine. Given with the food to men and dogs, it is simply absorbed and excreted again : even 15 grm. in three days are nearly completely excreted in the urine. The behaviour of taurine in the herbivora is quite different. Introduced into the stomach, three quarters of it is consumed and one quarter of the sulphur is found as thiosulphate and one half as sulphate in the

urine, the bases of these salts being provided by the body.   A year later Salkowski (15) examined the action of taurine on animals very fully : he showed that rabbits were easily killed by moderate doses of it, and attributed the poisoning to a withdrawal of the fixed alkalies from the tissues.   If alkali was given along with the taurine the animals did not die.   He showed that rabbits are easily poisoned by dilute sulphuric acid, but again if an animal which had received a fatal dose of acid was fed at once on an alkaline food such as potato it recovered completely.   Lassar (16) determined the alkalescence of the blood of normal and acid treated animals, and found that in rabbits the alkalescence was much depressed, but in dogs and cats it was much less depressed.   He concluded that the acid removed bases from the body ; but in the case of dogs and cats the amount of acid he gave was so large that, if it had all been absorbed and excreted as salt, it would have more than sufficed to render the whole animal 'acid'. Accordingly it can scarcely be doubted that the organism possessed a regulatory mechanism for the acid-base equilibrium.

Walter (17), who also investigated the action of acids upon animals, after discussing various ways of expressing the action quantitatively, considered that the carbonic acid content of the blood must be proportional or very nearly so to its content in alkali, and therefore decided to determine the carbonic acid of the blood in his animals.   His experiments were made on rabbits and dogs, and the acids he employed were hydrochloric, phosphoric, salicylic, hippuric, and succinic. Since these experiments are of importance for the later discussion, I give a table compiled from Walter's results in the case of rabbits:

Acid given.	Weight of acid given per kilo animal: grm.	Soda (Na$_2$O) equivalent of acid given.	Volume of CO$_2$ at 0° and 1000 mm. in 100 vols. blood.	Result.
None	—	—	26·86	—
Hydrochloric	0·53	0·45	16·40	Recovery
Hydrochloric	0·81	0·69	8·83	Recovery
Hydrochloric	1·00	0·85	2·54	Death
Phosphoric	3·56	1·12*	2·07	Death
Salicylic	2·10	0·47	11·20	Death
Hippuric	9·00	1·56	—	No effect at all
Succinic	9·00	2·36*	—	No effect at all

* Both calculated for the monosodium salts, so that these figures are really rather too low.

Of these acids, hydrochloric is by far the strongest, and it is characterized by its swift and sharp action—a rabbit will recover after a dose of 0·8 grm. per kilo body weight, but it will die in a few hours after a dose of 0·9 grm. per kilo. Phosphoric acid in half normal solution is about one-sixteenth as strong as hydrochloric acid of the same concentration, and its alkali equivalent, even supposing that it only has one of its three hydrogen atoms replaced, is 1·12 as against 0·85 for hydrochloric acid at the lethal dose—that is, higher by one-third.   Salicylic acid may be regarded as about equal in strength as an acid to phosphoric, perhaps it is a slightly stronger acid, and it evidently acts as an acid, for it reduces the carbon dioxide quite analogously to hydrochloric acid at the same

alkali equivalency. But with the carbon dioxide at 11·2 volumes in pure acid poisoning a rabbit would live. Walter's results, therefore, with this acid show that it has a specific toxic action apart from its action as an acid. The other two acids, although administered in much larger doses than the hydrochloric acid, were entirely without action. Hippuric acid is probably not changed in the organism of the rabbit, and although it is sparingly soluble in water, its salts are very readily soluble ; unfortunately Walter does not state whether hippuric acid was found in the faeces of his animal. Probably a good deal of the succinic acid was metabolized. Now the strengths of these two acids are comparable with those of acetoacetic and β-oxybutyric acids (18).

Acid.	Strength of Acid (K).
Hippuric	0·000222
Acetoacetic	0·000150
Succinic	0·000066
β-oxybutyric	0·000020

From this early work of Walter it is plain that on considering the action of acids on animals the character of the anion must be taken into account as well as the strength of the acid. Dogs behave very differently from rabbits towards hydrochloric acid ; thus an 8·5 kilo dog took 16 grm. of hydrochloric acid in four days, receiving 8 grm. on the first three days and 8 grm. on the fourth day. Its carbon dioxide was only reduced to 18·04 volumes, that is, not more than 10 per cent. by a dose of acid per kilo of animal double the lethal dose for rabbits. He finds this result is due to the fact that the dog has the power of producing ammonia, with which it neutralizes the acid to a large extent. Thus :

Mean daily excretion of ammonia on 4 days without acid 0·574 grm.
„   „   „   „ 5 „ with   „ 1·308 „

Therefore excess of ammonia on the five acid days = 5 × 0·734 = 3·670 grm. The amount of hydrochloric acid given was 10·92 grm. Now 3·67 grm. of ammonia neutralize 7·88 grm. of the acid, so that 72 per cent. of the acid given was neutralized by the ammonia. In a second experiment 74·8 per cent. of the acid was neutralized. Finally, in the case of rabbits poisoned by hydrochloric acid, the rapidity of recovery on administration of alkali must be noticed. An animal is near death, having received more than 1 grm. hydrochloric acid per kilo of body weight, when half a grm. of sodium carbonate in 5 per cent. solution is injected into the jugular vein—in ten minutes the heaving of its flanks has diminished considerably, the heart action is powerful, the pulse distinctly numerable; in one hour the breathing is quiet and nothing amiss can be found with the animal; or again, double the fatal dose of acid may be given without any symptoms of poisoning at all if a solution of sodium bicarbonate (0·8 grm.) is injected subcutaneously after the acid has been administered.

The next advance towards the discovery of hydroxybutyric acid was made by Coranda (19) and Hallervorden (20). Coranda fed Hallervorden on a constant diet of meat, bread, milk, and beer for twelve days, and gave him 2·81 grm. of

pure hydrochloric acid on the seventh and eighth days : his mean ammonia excretion before receiving the acid was 0·819 grm. a day ; after the acid it was 1·239 grm. per day for five days, and normal again on the twelfth day. Two points are worth remark : first, the duration of the effect of the acid, its action extending over three days after the second dose ; and second, the response of man to acid poisoning is like that of the carnivora. Hallervorden made a thorough examination of the excretion of ammonia in various diseases in man. In diabetes he finds the amount to vary greatly from case to case : thus in nine cases it varies from 0·13 to 5·96 grm. a day. In one of his cases (K.) the amount varied from 3 to 5·96 grm. daily by the month together, and in three other cases it was nearly as much ; such amounts as these he designated as a ' colossal abnormality '. He points out that the cause of the high ammonia excretion in diabetes must be sought in a high excretion of acid. Diabetics are known, he says, to excrete much phosphoric acid, but he finds no parallelism in his cases between the amount of this acid and the ammonia ; and he goes on to point out that not only inorganic acids, but lactic, glycuronic, or other such acid products of sugar metabolism, may unite with the ammonia and lead to its excretion. Magnus-Levy (6) states that Hallervorden believed the acids concerned were inorganic! It is also worth while to point out that Hallervorden gave large doses of sodium bicarbonate to one of his patients, and showed that it had practically no effect on the excretion of ammonia.

The same year in which Hallervorden published his results a paper appeared by Gaethgens (21) recording some most careful experiments on the administration of sulphuric acid to a dog. The animal was fed on a uniform diet throughout each experiment : there was a fore-period, an acid period, and an after period, each of three days. Determination of all the chief acids and bases of the urine were made each day, and to obtain comparable results each acid and base was calculated in terms of its sodium equivalent. His results showed that when sufficient acid was given to increase the acid excreted by more than three times the normal, there was nevertheless sufficient base excreted to neutralize the acid, but very little of the extra acid was neutralized by the fixed bases ; nearly all of it was neutralized by ammonia. Thus on a normal day the ammonia accounted for 40 per cent., and the fixed bases for 60 per cent., of the total bases, while the average of the days under the influence of the sulphuric acid was ammonia 66 per cent., fixed bases 34 per cent. He points out that this production of ammonia explains the immunity of the dog from acid poisoning, for by its union with ammonia the acid is prevented from withdrawing from the organism the fixed alkalis which are indispensable for the life processes. Then he depletes his animal's store of ammonia by feeding it for eight days on an ' acid food ', and shows that by giving acid he can cause the acid equivalent to exceed the base equivalent and cause also a large increase in the excretion of the fixed bases ; while in the former experiment the fixed bases only rose by 6 per cent., they now rise by 64 per cent.

These two researches appear to have led directly to the great work of

Stadelmann (22). In this he examines the urine of ten diabetic patients, and shows that in several of them abnormally large amounts of ammonia are excreted. Following Gaethgens, he decided to determine all the important bases and acids in the urine of a suitable case and to express them all in terms of their sodium equivalents. Three cases are conceivable :

1. The acid and base equivalents may be approximately equal.
2. The base equivalents may exceed the known acid equivalents.
3. The acid equivalents may exceed the base equivalents.

Stadelmann found that in a patient with an acid urine and a high ammonia excretion case 2 corresponded to the observed facts. I give his figures for one day :

Case X. Man, age 19.   24/xi/81.   Vol. urine 10,730 c.c.

Acids. Sodium equivalent.	Bases. Sodium equivalent.
SO_3 = 2·1933	Mg = 0·5409
P_2O_5 = 0·9647	Ca = 0·2101
HCl = 11·5345	Na = 11·0631
H_2U. = 0·2904	K = 3·3730
————	NH_3 = 5·8479
14·9829	————
	21·0350
	14·9829

Excess of base equivalent = 6·0521

From such figures as these he concludes that a diabetic urine which, like the one under examination, is strongly acid and contains a large excess of bases and particularly of ammonia, must contain some unknown acid in considerable quantity. He next undertook an analysis of his own urine for a period of five days, and obtained each day an excess of acids over bases, the lowest excess expressed as sodium equivalent being 0·3325 and the highest 0·4872. This result confirmed him in his opinion as to the existence of an unknown acid in such a diabetic urine as the one examined, and he sought to isolate and identify it. He showed that the acid cannot be distilled from the urine. After many trials he succeeded, by evaporating the urine to a syrup, extracting with alcohol, removing the alcohol, acidifying, extracting with ether, and converting the extract first into the barium salt and then into the zinc salt, in preparing a well crystallized salt. This salt was undoubtedly zinc β-hydroxybutyrate ; but he could not purify it sufficiently for analysis by any ordinary method. He therefore treated it with sulphuric acid and distilled it in steam, and was able to prepare a zinc salt easily and in large quantity from the distillate. This salt he analysed and showed to be zinc crotonate. He believed crotonic acid to be the acid he was seeking. It is astonishing that so competent an observer could have made such a mistake: he shows by many experiments that the acid peculiar to diabetic urine cannot be distilled from the urine ; he prepares the zinc salt of this acid, treats it with sulphuric acid, and obtains an acid which distils readily in steam, and yet concludes that the two are identical !

The amount of acid he isolates from the urine he describes as 'simply colossal'.   After referring to the ferric chloride test for acetoacetic acid and to the view held by many that this acid is the cause of diabetic coma, he states that his results have no relation to this acid, for, in spite of the considerable amount of crotonic acid present in the urines he examined, they mostly gave no ferric chloride reaction.   His Case X, which gave the 'colossal' amounts of crotonic acid, never showed the ferric chloride reaction, and the patient died in coma : also he states that others, but he does not say what others, have observed cases of diabetic coma in which the urine gave no ferric chloride reaction.   I emphasize this point because Magnus-Levy, as will be seen later, also disparages the importance of acetoacetic in diabetic urine, and emphasizes the importance of β-hydroxybutyric acid.   Stadelmann's failure to obtain the ferric chloride reaction in his Case X is, I believe, easily explicable: his patient passed an enormous volume of urine very rich in sugar—for example, he records the urine for sixteen days only of his Case X, and I find the average daily urine to be 10,080 c.c. and the average percentage of sugar to be 7·3.   The ferric chloride reaction is not a sensitive one under these conditions.   Stadelmann never *determines* the acetoacetic acid.   After emphasizing the amount of his acid which may be present in certain cases he draws attention to the similarity of the symptom complex of diabetic coma to that of acid intoxication as it is known from the work of Walter, and definitely adopts acid intoxication as the cause of diabetic coma.   Man, from the work of Coranda, appears to resemble the carnivora inasmuch as he can produce large quantities of ammonia, as is evident from the work of Hallervorden and Stadelmann, in order to neutralize an acid when it arises in diabetes.   In a later paper Stadelmann raises an objection to Coranda's view on the ground that in man the excretion of ammonia is extra-ordinarily labile—it may rise from about 2 grm. on one day to 12 grm. on the next, that is, fivefold in twenty-four hours.   He here evidently refers again to his Case X, and I give his actual figures :

	Vol. of urine.	Reaction.	Sugar. %	Total.	NH_3.
19/xi/81	11,360 c.c.	Acid	7·0	794·8	2·921
20 ,, ,,	11,150 c.c.	Neutral	7·6	847·4	12·243
21 ,, ,,	11,200 c.c.	Weak alk.	8·0	896·0	3·045

It will be seen that the rise is only a shade over fourfold ; also it will be seen that no other quantity varies in a manner at all comparable with the ammonia ; and finally, Stadelmann regards the ammonia as a rough measure of the diabetic acid, so that from one day to another we should here have a rise of acid expressed as hydroxybutyric of 55 grm.   It is obvious that about 9 of the 12 grm. of ammonia are due to Stadelmann and not to his Case X.   Having definitely committed himself to the acid intoxication theory he suggests the treatment by alkali, and to obtain quick and direct action he suggests that it should be given by injection into a small vein as far removed from the heart as possible and in the form of a 2 or 3 per cent. solution of sodium carbonate.   He

shows (23) that 20 grm. of sodium carbonate (Na_2Co_3) can be given in this way without injury to a 9 kilo dog, and suggests that 140–160 grm. could be given to a 60 to 70 kilo man. It is singular that he does not appear to practise the intravenous injection of sodium carbonate himself. In a later paper (24) he still gives it by mouth, and he shows that by continued administration of large quantities it is possible to reduce the excretion of ammonia in a severe case much to the advantage of the patient, and that when the drug is discontinued the ammonia reappears and with it the unfavourable symptoms.

Among Stadelmann's cases was a boy of about sixteen (Case IX) who, in April, 1882, was passing between 1,400 and 2,000 c.c. of urine containing about 2 per cent. of sugar and about 1·5 grm. total ammonia. The urine, according to Stadelmann, did not give the ferric chloride reaction (but 100 c.c. of it on distillation with HCl always yielded a distillate which gave typical iodoform crystals). In the summer of 1883 the case returned to the hospital and was examined by Minkowski (25). The urine was now 5 to 6 litres, and contained 8 to 9 per cent. sugar and a total ammonia of 2 to 3 grm.; it also contained much acid. Minkowski extracted the acid, following Stadelmann's methods, and he prepared and analysed the zinc, sodium, and silver salts. From his analysis he calculated the formula, and recognizing Stadelmann's mistake concluded that the acid was not crotonic but hydroxybutyric. He compared the properties of the acid with the synthetic acid which had been prepared by Wislicenus, and concluded that they were identical: he also found that the acid yielded much acetone on oxidation with potassium dichromate and sulphuric acid, and on distillation with sulphuric acid alone showed that it gave crotonic acid. He failed to discover its optical activity. After the publication of Külz's paper he re-examined the acid and confirmed Külz's observation. That he did not obtain the acid very pure is shown by his low figure of $-20·6°$ for its specific rotation. Minkowski now points out that Stadelmann's Case X died in coma, and that his own case ends in the same way. Both patients excreted large amounts of hydroxybutyric acid, and this acid is related to acetone, a substance which Frerichs (26) points out is always demonstrable in the urine of patients who have died in diabetic coma. He is of opinion that none of the three substances, acetone, acetoacetic acid, hydroxybutyric acid, exerts a specific toxic action; the last, in particular, cannot be very toxic, for it has been shown to be present in the urine of patients in large amount and by the year together, without the appearance of any typical functional derangement. So Minkowski adopts Stadelmann's theory of acid intoxication, and at the latter's suggestion treats his patient when he passes into coma with large doses of sodium carbonate and bicarbonate. A few points in his description of the case are particularly worth remarking. The urine passed first after the onset of coma gave 'an intensely Burgundy red colour' with ferric chloride, and on distillation with hydrochloric acid much acetone. Three hours after the onset of coma 20 grm. of sodium carbonate in 200 c.c. of water are given by the sound, and a similar dose per rectum. In an hour and a half there was a marked improvement, and the two doses were repeated.

Some strongly acid urine was passed, and once more the two doses were repeated. The improvement is maintained until the following day. The urine is still acid and the ferric chloride reaction very intense. An estimation of the oxybutyric acid in the twenty-four hours' urine gave 24 grm., but in view of the faulty method it was no doubt a good deal more. In the course of the day the patient became worse, and in spite of a twice-repeated dose of 20 grm. of sodium carbonate and 2 grm. of potassium carbonate he died in the evening. Not all the sodium carbonate given was absorbed, but in the last twenty-four hours' urine there were about 13 grm. of sodium, which would be equivalent to nearly 59 grm of oxybutyric acid, if all of it, which would not be the case, was due to the sodium carbonate.

It ought to be mentioned that in his second paper Minkowski suggests that hydroxybutyric acid may be considered as derived from fat or from amino acids.

The point at which we have now arrived is this. Acetone and acetoacetic acid had been known to occur in the urine of severe diabetic cases for some time, but they were not regarded as being very toxic. The laevo-rotatory hydroxybutyric acid has now (1884) been discovered in such urines and in very large amount. Stadelmann, inspired by the work of Walter and of Hallervorden, has adopted the theory of acid intoxication, and, as a natural consequence, following Hallervorden, has prescribed alkali for the treatment of the condition. There is no doubt that his cases benefited by the alkali as he gave it, but when alkali is given to a case actually in coma by Minkowski it fails to produce more than a transient improvement.

So far no systematic determinations of hydroxybutyric acid had been attempted : the first to make such an attempt was Wolpe (27). His method gave 90 per cent. of the acid added to a urine containing sugar, and with slight modification it was the method employed by Magnus-Levy for determining the acid by extraction. Wolpe adopts the theory of acid intoxication, and treats his patients with large doses of soda—for example, a patient threatening to go into coma is given 200 grm. of the bicarbonate per rectum, but without effect : two hours and a half later she is given 1 litre of 3 per cent. carbonate (Na_2CO_3) by injection into an arm vein, yet death ensues in four hours. The injected carbonate would neutralize 58·8 grm. of hydroxybutyric acid. The acid excreted on the preceding day was 22·8 grm. Wolpe does not observe any parallelism between the amount of acetone and that of the hydroxybutyric acid, but he recognizes a parallelism between the acetoacetic acid, as judged by the ferric chloride test, and the hydroxybutyric acid. After Wolpe's paper there are no important determinations of hydroxybutyric acid, until the first of Magnus-Levy's (6) papers appeared. But in the meantime several papers of great importance for Stadelmann's theory of acid intoxication appeared. Only one of these need be mentioned now—a paper by F. Kraus and G. Honigmann (28). In it the whole subject of acid intoxication is reviewed with an excellent bibliography. Acid products of intermediate metabolism may be formed more abundantly than is

normally the case : a gradual or a sudden retardation of the oxidation of certain definite acid compounds may occur—under these conditions acid auto-intoxication will occur.   In this case the toxicity of the acid is of importance : the protective arrangements of the organism are also important.   When the capacity of the latter to deal with the acid is exceeded binding of fixed alkali occurs, and finally, through the intervention of the secreting tissues, actual withdrawal of fixed alkali occurs.   They then show the importance of the alkalis and alkaline salts for the maintenance of life.   Simple tests for the diagnosis of an acid intoxication are indicated.   If attention is to be directed to the binding of alkali this may be ascertained by two methods—by titration, and by a determination of the total carbonic acid of the blood.   Of these two they regard the latter as better suited to indicate the diminution of the content of the blood and tissues in alkaline compounds.   A diminution of the total carbonic acid of the blood indicates a binding of the alkali by other stronger acids.   Minkowski (29) had made determinations of the blood carbonic acid in diabetic coma : in a non-comatose case he found 17 per cent., but three weeks later in coma 3·3 per cent.   Kraus himself made determinations in thirteen cases of diabetic coma and found 9·83 : 10·20 : 10·50 : 10·59 : 12·44 : 15·50 : 17·40 : 18·50 : 19·33 : 19·38 : 19·54 : 19·62 : and 19·77 volumes per cent. at 760 mm.   Kraus and Honigmann make a careful comparison of the symptoms of acid poisoning and diabetic coma.   The similarities are the peculiar dyspnoea, the accelerated pulse, the fall of temperature, the cessation of the respiratory before the cardiac activity.   They say that these points of contact place the acid intoxication theory of diabetic coma far ahead of all other theories, but that the whole clinical picture is caused by acid poisoning in the strict sense of the term is little probable.   They have tried the action of soda by injection into the veins, and by administering it subcutaneously, and by the bowel, in the amounts prescribed by Stadelmann, on twelve cases.   A transitory improvement was effected, but the urine showed continuous acid reaction, and the fatal issue was not averted.

The theory of acid intoxication now received the vigorous support of Magnus-Levy in two very long papers (6), (11), which appeared in 1899 and 1901 respectively.   These two papers have had considerable influence on both the theory and treatment of diabetic coma.   In them Magnus-Levy attempts three things :

1. To show that diabetic coma is an acid poisoning.
2. To show that the acid which effects the poisoning is hydroxybutyric acid, the acetoacetic acid being a very variable quantity of little significance—in so far as it is present it too acts only as an acid.
3. To trace the origin of hydroxybutyric acid and, therefore, of its supposed derivatives, acetoacetic acid and acetone.

1. Under this head Magnus-Levy states that the symptom complex of this coma is similar to that observed in the experimental acid poisoning of rabbits. As we have seen, Kraus and Honigmann had already shown what symptoms are common to the two conditions.   If the two states are really alike, then the action

of alkali upon them should also be alike. After a lethal dose of acid an equivalent dose of soda given to the rabbit that received the acid will cause the animal to make a complete recovery in an hour. It is perhaps too much to say that a human being never has made a complete recovery from diabetic coma under the influence of administered soda, but it is not too much to say that many competent observers have completely failed to restore their patients by the use of soda. Fourteen examples of this failure have been given, and others will be referred to below.

Then Magnus-Levy proceeds to reason as follows. According to Walter, 0·9 grm. hydrochloric acid per kilo body weight will cause the death of a rabbit by acid poisoning, but the molecular weight of hydroxybutyric acid being higher than that of hydrochloric acid in the ratio of 104 to 36·5, it will require 2·6 grm. of this acid per kilo to poison the rabbit, supposing the two acids to be of equal avidity, or, assuming the same ratio of acid to body weight to be required to poison a human being, then a youth of 30 kilos would require about 80 grm., or an adult of 60 kilos would require at least 160 grm. of the acid for fatal acid poisoning. A smaller amount would be sufficient if the body had been depleted of its alkali by previous chronic acid intoxication; while a larger amount would be necessary if the body had ammonia at its disposal for the neutralization of the acid. Magnus-Levy set out to find these large amounts of acid in the urine, and he found them in two cases, one in each of his papers. These large amounts of acid must require equivalent amounts of alkali for their neutralization so that the alkalescence of the blood in a body excreting them must be much diminished. Alkalescence determinations are made, by the method of Loewy (30), on the blood of diabetic patients, with the result that at incipient coma there is only a slight diminution or none at all, but as coma deepens there is, even when bicarbonate of soda is given, a fall in the alkalescence. Thus:

		Alkalescence (grm. NaOH in 100 c.c.).
Beginning of coma	18/iii 3 p.m.	361
Coma advanced	19/iii 9 a.m.	234 (72 grm. NaHCO$_3$ given)
Beginning of coma	12 noon	324
In coma	7 p.m.	362 (200 grm. NaHCO$_3$ given : coma improved, but patient died)
Five days before coma		298
Coma advanced		124 (No NaHCO$_3$ given)

In his first paper Magnus-Levy describes six coma cases. The highest hydroxybutyric acid figure, as obtained by actual extraction of the acid in the first five cases, is 26·4 grm. : the highest figure obtained by the excess of base method in the same five is 40 grm., and this includes the acetoacetic acid. All these cases were fatal. The sixth case was a boy thirteen years old suffering also from nephritis and passing much albumin : he had two attacks of coma separated by an interval of three weeks, and he recovered from both of them. The subsequent history is not given. I give a part of Magnus-Levy's figures for this case, for comparison with some of my own and others.

Date.	Urine. Lits.	Sugar.	N.	N as NH_3.	Acetone as aceto-acetic.	Hydroxy-butyric* ex-tracted.	Hydroxy-butyric and aceto-acetic by base excess.	P_2O_5.	$NaHCO_3$ given.
5/vii/98	6·5	195	19·1	2·07	18·3	49	74	3·75	60 Coma begins
6 ,, ,,	8·0	200	18·8	2·10	32·9	70	109·5	2·64	210
7 ,, ,,	9·2	143	15·1	2·32	23·6	101	157·1	1·30	90
8 ,, ,,	6·4	67	9·4	2·37	25·6	49	88·4	0·57	80
9 ,, ,,	6·8	135	14·6	3·07	27·9	—	98·7	1·66	60 Coma over

* The values in the original paper were calculated on Minkowski's value for the specific rotation of oxybutyric acid. I have recalculated them, using the correct specific rotation as determined by Magnus-Levy.

Why is there this enormous difference in the amount of acids excreted by the first five cases and the sixth, and why is there such a difference in the issue? It is not due to the bicarbonate in all cases, for several of the fatal cases had enormous amounts of the drug; e. g. Case IV, a woman of only 32 kilos, the same weight as the boy, Case VI, had 40 grm. of it daily for six days before coma appeared, and during coma an intravenous injection was given without effect. The explanation, according to Magnus-Levy, is that in the first five cases the acids are formed but cannot be excreted; they remain in the tissues. ' The diabetic dies, not from the acid excreted in a neutralized state in the urine, but from that left in the body which he has not the power wholly to neutralize.' He recognizes the difficulty of assuming that the acids can be free in the blood, and to surmount it he assumes that the base required to neutralize them is withdrawn from other compounds important for life—the carbonates and proteins. The free acid, he says, is not excreted in the urine, and its sodium salt is not excreted quickly enough, slower in fact than it is formed. Accordingly he examines the organs of his Case II for hydroxybutyric acid, and finds most in the blood, which contains ' >2·2 per mille '; the spleen comes next with ' >1·7 per mille '. '*In toto* there was present in this case of 45 kilos weight at least 100 grams of acid.' That is, to obtain the 100 grm., Magnus-Levy assumes the whole body to contain the same percentage of oxybutyric acid as the blood, for $2·2 \times 45 = 99$. Here, also, Magnus-Levy disparages the importance of acetoacetic acid: it only forms one-tenth of the hydroxybutyric acid and certainly shares to only a small degree in the acid poisoning. To complete his argument for acid poisoning he now considers the body's store of alkali; for this he takes the alkalescence of the whole body as equal to that of the serum, namely, 0·125 grm. NaOH for 100 grm., this being the amount found by Spiro and Pimsel, Kraus, and others.[1] Now death occurs in rabbits, and presumably in man, when half the 'native alkalescence'—this is the value found by direct titration with an acid and indicator, and corresponds, according to Spiro and

[1] These authors worked with horse and pig's blood chiefly.

Pimsel (31), to the alkalescence of the carbonates and phosphates only, or, what is the same thing, to the 'diffusible alkali '—is exhausted.   There is thus a store of $0.125 \times \dfrac{50{,}000}{100} \times \dfrac{1}{2} = 31.25$ grm. NaOH at the most available for neutralization in a body of 50 kilos, and it could neutralize 81 grm. of hydroxybutyric acid.   It is plain, therefore, that on long-continued production of large amounts of acid the neutralization must be effected by ammonia.   So in cases of severe diabetes much ammonia is found in the urine, and quantities above the normal 1 grm. or so a day neutralize the acetoacetic and hydroxybutyric acids, and in fact give a rough measure of them.

Apparently only the titratable alkalescence of the blood is allowed by Magnus-Levy to be of any account in settling the diminution of alkalescence : the carbon dioxide of the venous blood, which had been determined by Kraus, 'is only the partial expression of the diminution of the active blood alkalescence '. Biernacki (32), in a paper which appeared two years before Magnus-Levy's, had pointed out that no two methods of determining blood alkalescence agreed, and further that such determinations were of little use, if not quite worthless.   As regards Magnus-Levy's remarks on the carbon dioxide of the blood, the only conclusion I can draw from them in the light of what has been said already is that because this author did not use this method it is *ipso facto* a worthless method.

2. In the urine of a severe diabetic only two organic acids are known to occur in large amounts, the two already referred to.   Small amounts of formic, acetic, butyric, and hippuric acids are also present, but they are negligible in comparison with the other two.   I may remark here that I can confirm the presence of formic acid, but I have never obtained a trace of butyric acid, nor have I ever obtained hippuric acid from any of my extracts.   In place of hippuric acid I have repeatedly obtained benzoic acid, in perfectly pure condition : it may have been formed by the hydrolysis of hippuric acid during the extraction, but I do not think so.   Of the two chief acids Magnus-Levy believes hydroxybutyric acid to be by far the more important in causing the acid poisoning.   He refers to Stadelmann's failure to obtain the ferric chloride reaction even when the urine contained much ammonia and therefore much hydroxybutyric acid.   When large amounts of acetone are found it is true that very large amounts of hydroxybutyric acid are also found, but there is no real parallelism between them.   Acetone is not essentially concerned in the phenomena of coma, and the enormous and inexplicable oscillations in the amount excreted strongly reduce its value as a measure of impending coma.   Quantities of more than 6 grm., equivalent to 10.5 grm. of acetoacetic acid, are rare : the values he obtained in his Case VI are enormous and quite exceptional.   Although the amount of hydroxybutyric acid may be very high, as in the Case VI, which is the highest amount ever observed by any one, yet its percentage amount has been fixed as to its upper limit by Magnus-Levy.   He has never observed out of coma a higher percentage than 0.6 : in coma, quite exceptionally, it may be 1.5.   All

higher percentages than these are calculated from the rotation of the fermented urine and are invalid. The futility of these remarks will appear from an examination of the cases here recorded.

3. That the acetone bodies do not arise from sugar is taken for granted: that they do not arise from protein, but that they do arise from fat, is what he would prove. Thus in 100 grm. of protein there are 53 grm. of carbon and 16 grm. of nitrogen: 12 grm. of this nitrogen are excreted as urea, 2·4 grm. of it as ammonia, and 1·6 grm. of it as other compounds. The 12 grm. of urea nitrogen and the 1·6 grm. of N in the form of other nitrogenous compounds are united respectively with 5 and 2 grm. of carbon. So these 7 grm. are deducted from the 53 grm. of protein carbon—on what grounds we are not told. Surely some, if not all, of this carbon would be due to sugar or fat. Allowing these assumptions we have from 100 grm. of protein, 46 grm. of carbon at the most available for acid production: then since 100 grm. of hydroxybutyric acid contain 46·2 grm. of carbon we may assume 100 grm. of protein can form at most 100 grm. of the acid. Calculating the urinary nitrogen into its equivalent of protein Magnus-Levy now arrives at the following figures, which for the sake of clearness I put into a table :—

| Date. | Urinary nitrogen. | | Acids. | |
	As such.	As protein.	Calculated from protein.	Found in urine.
6/vii/98	18·8	117·5	117·5	115·4
7 ,, ,,	15·1	94·4	94·4	142·6
8 ,, ,,	9·4	58·8	58·8	83·0
			270·7	341·0

Thus the amount of acid found, especially if the breath acetone be added in, enormously surpasses the calculated quantity. But these figures are entirely misleading. I recalculate the last two columns on the assumption that 50 grm. of the protein carbon are available for acid production, and introducing the correction referred to on page 312, thus :—

| Acids. | |
Calculated from protein.	Found in urine.
127·2	102·9
102·2	124·6
63·7	74·6
293·1	302·1

the difference is by no means so striking. It is no doubt true, as Magnus-Levy remarks, that these tables take no account of the sugar formed from protein, so that it remains impossible to account for the acids found by him on the theory that they are entirely derived from protein; but the corrected table shows that the carbon of the protein is not so inadequate as Magnus-Levy would have us suppose, the discrepancy having fallen from 70 to 9 grm.

That the acetone bodies might arise from protein or fat was, as we have seen, suggested by Minkowski : that they are very probably formed from fat or

from compounds containing two carbon atoms which arise in the breakdown of fat was first suggested by Geelmuyden (33), and as he used butter as his chief fat he thought the lower fatty acids of butter might be responsible for most of them.   Magnus-Levy suggests that fat is the source of the acetone bodies, and shows that for the large amounts of the substances found by him the lower fatty acids of such fats as butter will not suffice : nor will the assumption suffice that from one molecule of fat made up, say, of one molecule of glycerol, and one each of palmitic, stearic, and oleic acids only one molecule of hydroxybutyric acid is produced from each fatty acid molecule.   The long chains of carbon atoms of the higher fatty acids must be so far disintegrated that from one such chain more than one molecule of hydroxybutyric acid can be produced.   It is advisable to see where the assumption of the production of these stupendous amounts of acid from fat will lead us.   Let all the carbon of the fatty acids in a fat such as the one referred to above be converted into hydroxybutyric acid : thus 1 grm. of fat would yield 1·57 grm. of it.   In Magnus-Levy's Case VI there were produced acetone bodies equivalent to 124·6 grm. of butyric acid (157 reckoned by the base excess method which Magnus-Levy regards as the more accurate one) on one day ; that is, 79·5 grm. of fat would have to be transformed without any gain to the body, for the glycerol fraction of the fat would presumably be converted into sugar.   To derive all the acetone bodies from fat seems as unfeasible as to derive them all from protein.   In estimating the value of Magnus-Levy's contribution to our knowledge of the acetone bodies in diabetes it should be pointed out that in both his great papers he describes twenty-five cases in which determinations of the hydroxybutyric acid are made : the total number of determinations on these cases is 46 by extraction of the acid, and 15 of these are incomplete, and 39 by the method of base excess ; of the 31 complete extractions 6 were done on one case and 10 on another, that is, over half of them were done on two cases : of the 39 determinations by base excess 13 were done on one case and 13 on another.   There is in no single case any diet given : the nearest thing to a diet being that 'about four litres of milk ' were taken.   Ten of his cases are severe coma cases, and eight of them die in spite of enormous doses of soda, and two are ' cured ': certainly some of these cases were brought in practically comatose, but there are cases he ' observed ' for months. It is Magnus-Levy's great service that he first prepared crystallized hydroxybutyric acid and determined the specific rotation of the acid correctly, and that he again drew attention to the large amounts of hydroxybutyric acid which are often present in diabetic urine.   The methods he has published for its determination are impracticable for clinical purposes.

THE CASES.

I now proceed to the description of the results obtained from my own cases.

Case I.   J. H. B.   Age 28.   A medical man.

Noticed his loss of weight, a weakness in the legs, thirst, an increased appetite, and glycosuria two months before admission.   Admitted September 8, 1909.

No history of glycosuria in his family.   The organs appeared to be normal, except perhaps the liver, in the region of which there was some dullness.

In June, 1909, his weight was 12 st.: on Sept. 8 it was 9 st. 9 lb. (12 st. = 76·2 kilos, 9 st. 9 lb. = 61·2 kilos).   His weight during his stay in the hospital was as follows:

	st.	lb.		st.	lb.
September 8	9	9	November 1	10	8
,, 15	10	1·5	,, 8	10	10
,, 23	10	1	,, 15	10	13
,, 29	10	3·5	,, 22	10	13
October 4	10	5	,, 29	10	9
,, 10	10	8·5	December 6	11	0
,, 18	10	7	,, 13	11	1
,, 25	10	7			

He passed one or more stools every day except the following, when he passed no stool:

ix/9, 11, 12, 14, 18, 26, 27, 29.
x/1, 8, 12, 15, 20, 23.
xi/11. 15.
xii/11.

The accompanying table, Curve I, gives the volume, total sugar determined by rotation, total nitrogen, and total hydroxybutyric acid of the urine.   The hydroxy-butyric acid was determined by the method indicated in the appendix to this paper.   All these figures except the volume are plotted on Curve I—the nitrogen and hydroxybutyric acid being represented by their actual numbers, but the sugar by one-tenth:

Hydroxybutyric acid—dotted line } Actual figures.
Nitrogen—dashed line
Sugar—continuous line   One-tenth of the actual figures.

Crosses x on the curve indicate no determination.

The most striking feature of the curve is the high oxybutyric acid average from 13/ix to 30/ix.   It corresponds to the reduction of the carbohydrate in the diet.   On 10/ix B. took 1·13 grm. of white bread and on 21/ix all white bread was stopped.   During this period B. must have been in a very unstable equilibrium, bordering on an attack of coma.   The severe alternations in the curve from 15/ix to 17/ix are to be attributed to the test diet on which the patient was placed on those days.   The severe fall in the three substances determined on 24/ix is inexplicable, for the only remark B. makes in his notes is that he had beans for dinner.   This period, 13/ix to 30/ix, of this case should be compared with the early periods of S. G. and W. H. R., which are given later.   One ounce of laevulose was administered on 28/ix, and in accord with this there is a rise in the sugar and a fall in the acid excretion.

Through the great kindness of Dr. A. Harden, F.R.S., and Mr. W. J. Young, M.Sc. (34, 35), I was able to try the effect of administering to this patient their new compound hexosephosphoric acid.   This compound is formed when sugar undergoes fermentation by yeast or yeast-juice, and its production appears

to be an essential part of the fermentation process. As this substance had not been given to man before, I took on one day (16/ix) 21 grm. of the acid in the form of its sodium salt and made up to 270 c.c. At first the taste is unpleasant, but afterwards it is less so. There were no injurious effects of any kind. The highest dose given in one day to B. was 17·5 grm. of the acid neutralized as above. It was hoped that a substance such as this, which contains a hexose, and is an essential intermediate product in the resolution of the glucose molecule by a living organism, would enable us to administer a sugar to the diabetic in a combination which he could assimilate and catabolize. Unfortunately the 21 grm. of free hexosephosphoric acid only represent 11·1 grm. of sugar. The first dose of this compound contained 17·5 grm. of the acid neutralized by caustic soda, and B. took it on 30/ix. On the same day there is a marked fall in the excretion of oxybutyric acid and the fall continues slightly on the next day : then after a day when the acid was not determined, there is a further fall (3/x). The next dose of the sodium hexosephosphate was given on 4/x, but as B. objected to the taste of the compound he reduced the amount taken to half and took this amount also on 5 and 6/x with the result seen on the curve. After an interval of three days without the acid he took the same dose as before for four days, 10/x to 13/x; and this time the oxybutyric acid is at a slightly higher level. After consideration I am inclined to think that if the phosphate had not been given the excretion of acid would have been still higher, for it will be seen that B. is now on a very strict diet, and on such a diet it is not the way of oxybutyric to diminish. The hexosephosphate was next given :

19 to 25/x : 27 and 28/x : 3 and 4/xi : 28/xi : and on xii/1, 5, 8, 10, 12, 14, 16, 17, 19, 20, 21.

The last four were small doses of 5 grm. each.

From 19 to 28/x the oxybutyric acid keeps low except for two days, on 4/xi it is rather high again. Now except for one large dose on 28/xi, the effect of which is not apparent, no phosphate was given until xii/1. During this period the patient was given jelly (6/xi) containing in 284 grm. about 7 grm. of gelatine equivalent to 1 grm. of nitrogen. This substance was given as an agreeable change of diet and also in the hope that the glycocoll, in which gelatine is very rich, would favourably influence the oxybutyric acid excretion. Undoubtedly a change occurs in the latter excretion and it is a temptation to refer it to the glycocoll of the gelatine ; but if the effect in this case be compared with the effect produced in the case W. H. R., where 37·5 grm. of pure glycocoll were given on several successive days, the temptation is easily withstood. Starting on 13/xi carbohydrate was given in the form of potato : its effect on the excretion of sugar is clearly shown on the curve. There is a gradual increase in the amount of sugar excreted, clearly showing the very low tolerance for carbohydrate : but on 18/xi, where the potato was doubled, there is a sharp fall in the oxybutyric acid and practically no increase in the excretion of sugar. The rise of oxybutyric acid on 22/xi merely represents its return to the level of 15/xi ; but the rise of the following day is probably to be attributed to the five eggs taken on this day. Now we come to the last series of doses of sodium hexosephosphate : the dose of 1/xii is accompanied by a minute fall in the amount of the acid excreted, that of 5/xii by a marked fall, that of 8/xii by no change, that of 10/xii by no change, that of 12/xii by an apparent increase, and all the succeeding doses by a continuous fall. On 29/xi B. began to take one fair-sized baked apple whose weight, cored and ready for eating, he gave as 5·5 oz., and later he took two. At first the excretion of sugar continued to increase, but after 1/xii there is a marked fall to the level of the days which preceded the addition of potato to the diet. I believe that the carbohydrate of the apple is well tolerated by the diabetic, but I should not have expected it to cause an actual fall in the sugar excretion ; had the sugar remained at the level of 29/xi it would have called for no further comment. B.'s diet being so uniform

I am inclined to regard the hexosephosphate as a contributory cause of the decrease both in sugar and in oxybutyric acid. If the hexosephosphate is to be regarded as causing a diminution in both excretions it seems incredible that it can act solely in virtue of the small amount of carbohydrate it contains, and so it remains to attribute its action either to the phosphoric acid or to the combination of hexose and phosphoric acid. Reference will be made further on to the part played by phosphates in diabetic urine.

Finally, as regards the action of this substance, B. told me that when he first began to take it he experienced a comfortable sensation of warmth in his abdomen. When I took it I did not experience any such sensation.

Here I must record my deep indebtedness to Dr. Harden and to Mr. Young for allowing me to try their new compound on a diabetic and for the trouble they took in preparing large quantities of their unique intermediary product of the yeast plant metabolism.

It will be seen that 1 oz. of cream given 29/x to 4/xi (except 2/xi) had no effect in raising the excretion of the oxybutyric acid.
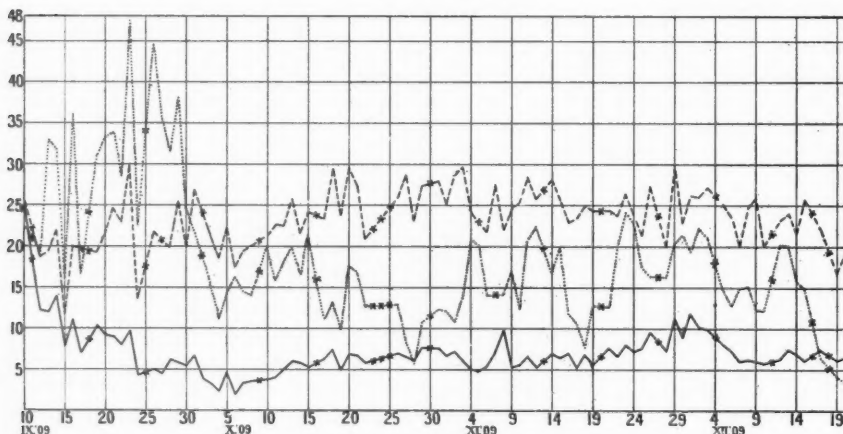
Curve I.   J. H. B.

The following particulars of his diet were written by B. himself, and he was certain of their accuracy. Here and there he records some of his symptoms. The twitching to which he refers was of the leg muscles. On his discharge he felt very well indeed. In the following spring he returned with a high hydroxybutyric acid excretion, often 50 grm. a day, but I was not able to do any determinations on him myself at this time. He was again discharged feeling quite well: he attended the Oxford and Cambridge Boat Race. About two years afterwards he died of diabetes in the West of England.

On admission, 8/ix/09, his diet was as follows :

Breakfast :   6 a.m.   1 egg : 2 rashers bacon : 6 thin slices bread and butter : tea with milk.

Lunch :   9 a.m.   2 or 3 slices of bread and butter : 1 cup of coffee with milk.

Dinner : 12.30 p.m.   Plate of meat (mutton, beef, chicken, or fish) : green vegetables : water or unsweetened lemonade.

Tea :   4 p.m.   1 egg : lettuce : watercress : mustard and cress : 4 slices bread and butter : tea with milk.

Supper: 7 p.m. Plate of meat (mutton, beef, chicken, or ham and tongue): lettuce : watercress: mustard and cress : 3 or 4 slices of bread and butter: water.

This diet was modified as follows:

10/ix/09. Custard, made with milk, at dinner : Casoid bread 8 oz. (226·8): white bread 4 oz. (113·4): started sod. bicarb. grm. 30 t. d. s. (5·8).

11/ix/09. Started tomatoes 1 at tea and 1 at supper: cheese for lunch : Callard's cocoa now and then in place of coffee or tea.

12/ix/09. White bread 3 oz. (85·0): extra butter 4 oz. (113·4): sardines occasionally at lunch or supper.

13/ix/09. White bread 2 oz. (56·7): sod. bicarb. gr. 60 t. d. s. (11·6).

14/ix/09. White bread 1 oz. (28·4): Casoid bread 16 oz. (453·6): sod. bicarb. grm. 60 five times a day (19·4): butter now 5½ oz. (156·2).

15 to 17/ix/09 (inclus.). A test diet as follows : Meat 9 oz. (255·2): vegetables 11 oz. (311·9): eggs 4: white bread 3 oz. (85·1): brandy 1 oz. (28·4 c.c.) with a very little milk.

18 to 20/ix/09. Same as 13/ix/09.

21/ix/09. All white bread stopped: sod. bicarb. 2 oz. five times a day (38·8).

24/ix/09. Paget's milk started in place of ordinary milk in tea, coffee, and cocoa: beans at dinner.

26/ix/09. Custard made with Paget's milk from this date onwards.

28/ix/09. Laevulose 1 oz. (28·4) on this day only.

30/ix/09. Took hexosephosphoric acid. (In future Hp. A. for short.)

4/x/09. Hp. A.

5/x/09. Hp. A. : sod. bicarb. 1 oz. five times a day (19·4).

6/x/09. Hp. A.

10, 11, 12/x/09. Hp. A.

13/x/09. Hp. A. : fish at supper : no lettuce during the day.

J. H. B. now records his diet nearly quantitatively. It is therefore tabulated and quantities are given in grm. and c.c. as far as possible. He took 19·4 grm. of sodium bicarbonate every day until 15/xii, when the dose was reduced to half. I regret that, in spite of the care that B. took to record his diet, I have found it impracticable to calculate it with sufficient accuracy in terms of carbohydrate, nitrogen, and fat ; for example, I have found that such items as chicken and mutton chops had been weighed—but with the bone.

OCTOBER.

	14	15	16	17	18	19	20	21	22	23	24	25
Eggs	2	2	2	2	2	2	2	2	2	2	2	2
Casoid Bread	453·6	453·6	453·6	453·6	453·6	453·6	453·6	453·6	453·6	453·6	453·6	453·6
Almond Bread												
Paget's milk c.c.	170	170	170	170	170	170	170	170	170	170	170	170
Mutton	170	227	113		142	+	170	170	113	170		170
Beef				142							142	
Chicken	+			113	113		142		142	+	113	113
Ham	+		113	28			28	113				
Fish						142						312
Cabbage		227				+						
Brussels Sprouts	227		170	85	113			170	170	170	170	
Lettuce / Watercress / Mustard and Cress	+	58	85	85	28	28	57					
Celery		85	85	28	+	57	57	57	85		28	
Tomato	3		1	2	2	2	2	2	1	3	3	2
Cheese	+	85		85	85		57		85		113	57
Bacon rashers	2	1	1	1	1	1	1	1	1	1	1	1
Marmalade (Callard's)	+		+	+		+		+		+		
Custard (made with P.'s milk)	170	170	170	85	142	+	170	454	454	454	170	454
Tea	+	+	+		+	+	+	+	+	+	+	+
Coffee or	+	+	+	+	+	+	+	+	+	+	+	+
Cocoa		0	0	0	0	+	+	+	+	+	+	+
Hp. A.												
Spinach							170					
Sardines												
Butter	About 150 grm. each day											
Cream												
Jelly												
Twitching				+ +	+ +	+ +	+	+	+ +	+ +	+	+
Thirst				0	+ +	+ +	+ +	+ +	+	0	+	0
Total urine c.c.	2,240	2,410		2,130	2,340	2,030	2,940	2,680	1,920			
Total sugar grm.	57·34	52·54		62·60	73·87	48·59	77·76	76·98	58·25			
Total nitrogen grm.	21·45	24·06		23·38	29·26	23·67	29·51	27·31	20·86			
Total B-oxy. grm. Rotation	16·71	21·28		11·00	13·21	9·97	17·55	16·77	12·70			

Phenolphthalein gr. v p.r.n. Castor oil ℥ 0·5

	October, 1909.						November, 1909.					
	26	27	28	29	30	31	1	2	3	4	5	6
Eggs	2	2	2	2	4	2	2	2	4	2	4	2
Casoid Bread, Almond Bread	453·6	453·6	463·6	453·6	453·6	453·6	453·6	453·6	453·6	453·6	453·6	453·6
Paget's milk	170	170	170	170	170	170	170	170	170	170	170	170
Mutton	142	170	170	340	170		113		113	255	227	227
Beef						170			42			
Chicken		ʹ+	142		142	170	170	227				
Ham												
Fish	170											
Cabbage		170	170	340	142		170		85	28	113	57
Brussels Sprouts	454	170	170		170	170	170	170	113		113	113
Lettuce, Watercress, Mustard and Cress										+		
Celery												
Tomato	2	2	4	2		1	2	1		3		2
Cheese	28			57		142	85	28		57	85	
Bacon, rashers	1	1	1	1	1	1	1	1		1	1	1
Marmalade (Callard's)			+	+		+	+					
Custard (made with P.'s milk)	170	454	170	113	113	113	170	170		113		170
Tea	+	+	+	+	+	+	+	+	+	+	+	+
Coffee or	+	+	+	+	+	+	+	+	+	+	+	+
Cocoa	0	+	+	0	0	0	0	0	+	+	0	0
Hp. A.												
Spinach												
Sardines	4	6			6			6				
Butter	About 156 grm. each day											
Cream				28	21	28	28		28	28		
Jelly												284
Twitching	+	+	+	+	+	+	+ +	+ +	+	0	+	+
Thirst	+	0	0	+	+	+	+	+ +	+ +	0	0	+
Total urine c.c.	2,100	2,590	1,870	2,310		2,330	2,090	2,360	2,300	2,160	1,900	2,050
Total sugar grm.	68·88	64·57	61·31	75·75		75·98	67·07	70·92	59·61	49·56	48·27	52·76
Total nitrogen grm.	25·93	28·72	23·06	27·43		27.96	25·16	28·64	29·66	24·13		21·81
Total B-oxy. grm. Rotation	12·89	8·32	5·74	10·68		12·27	12·13	10·76	13·83	20·87	20·06	14·10

Castor oil (Nov. 3)

NOVEMBER, 1909.

	7	8	9	10	11	12	13	14	15	16	17	18
Eggs	2	2	2	1	1	2	2	2	2	2	2	1
Casoid Bread	453·6	453·6	453·6	453·6	453·6	226·8	226·8	226·8	226·8	226·8	226·8	226·8
Almond Bread						226·8	226·8	226·8	226·8	226·8	226·8	226·8
Paget's milk	170	170	170	170	170	170	170	170	170	170	170	170
Mutton		227	113	113	227	113	113		113	113	113	198
Beef	113		57					198	85			
Chicken	113					113				113	57	
Ham					28	57	28	57	57		57	
Fish							113					85
Cabbage	57	170			227			57				
Brussels Sprouts	113	113		113		227				113	170	113
Lettuce												
Watercress												
Mustard and Cress												
Celery												
Tomatoes	2	1	1	2	1	1	2		1	1		1
Cheese	85		85	113		28				85		
Bacon, rashers	1	1	1	2		1	1	1	1	1	1	
Marmalade (Callard's)												
Custard (made with P.'s milk)												
Tea	+	+	+	+	+	+	+	+	+	+	+	+
Coffee or Cocoa	+	+	+	+	+	+	+	+	+	+	+	+
Hp. A.	0	0	0	0	0	0	0	0	0	0	0	0
Spinach			113				113	113				
Sardines				6	5							5
Butter	About 156 grm. each day											
Cream												
Jelly	284	284	284	284	568	568	568	568	568	568	568	568
Potato							57	57	57		57	113
Apple												
Twitching	+	+	0	0	+	+	+	+	+	0	+	0
Thirst	+	0	+	0	0	0	0	+	0	0	0	0
Total urine c.c.	2,425	1,900	2,060	2,300	2,940	2,460		2,860	2,720	2,280	2,270	2,445
Total sugar grm.	69·77	57·28	53·02	54·63	64·52	52·70		68·72	65·36	69·60	51·96	68·14
Total nitrogen grm.	27·64	22·00	24·49	25·34	28·40	25·83		28·11	25·63	22·86	23·36	24·92
Total B-oxy. grm. Rotation		14·17	17·00	12·35	20·54	22·38		16·78	19·85	11·82	10·63	7·91

NOVEMBER, 1909.

	19	20	21	22	23	24	25	26	27	28	29
Eggs	3	3	1	1	5	2	1	1	1	2	2
Casoid Bread	226·8	453·6	226·8	226·8	226·8	226·8	226·8	226·8	226·8	226·8	453·6
Almond Bread	226·8		226·8	226·8	226·8	226·8	226·8	226·8	226·8	226·8	
Paget's milk	170	170	170	170	170	170	170	170	170	170	170
Mutton	113		85	170	113	198	113		198		113
Beef	28		113		57	14	57	113		113	85
Chicken		113 ?								113	85
Ham		85						85	57		
Fish		57	85	85			28	57	85 ?		
Cabbage	113								170	142	142
Brussels Sprouts		57·	85	57	28		85	113			
Lettuce											
Watercress											
Mustard and Cress											
Celery											
Tomatoes											
Cheese		57	28	57		28		28			
Bacon, rashers	1	—	—	—	1	—	—	— +	—	1	1 +
Marmalade (Callard's)											
Custard (made with P.'s milk)											
Tea	+	+	+	+	+	+	+	+	+	+	+
Coffee or	+	+	+	+	+	+	+	+	+	+	+
Cocoa	0	0	0	0	0	0	0	0	0	+	0
Hp. A.										17·5	
Spinach	Incomplete					113					
Sardines							5				
Butter	About 156 grm. each day										
Cream											
Jelly	284	284	568	568	—	568	568	568	—	568	568
Potatoes	57	—	57	57	57	57	57	57	57	57	28
Apples											156 grm.
Twitching	0	0	+	0	+	+ +	+	—	0	+	0
Thirst	0	0	+	+	+	+	+	—	+ +	+	+
Total urine c.c.	2,360		2,440	2,410	2,870	2,750	2,540	2,830		2,156	2,960
Total sugar grm.	57·27		76·10	66·25	79·80	71·94	76·45	96·22		72·55	112·44
Total nitrogen grm.	24·38		24·36	23·68	26·44	23·87	21·30	27·34		20·04	29·71
Total B-oxy. grm.Rotation	12·72		12·65	19·98	24·15	22·69	17·48	16·37		16·37	16·26
	Naphth. tetrachler.	Naphth. tetrachler.			Naphth. tetrachler. gr. vii.	Naphth. tetrachler. gr. xiv.	Naphth. tetrachler. gr. xxvii.				

A a 2

	Nov., 1909.	December, 1909.									
	30	1	2	3	4	5	6	7	8	9	10
Eggs	2	1	1	1	2	1	2	3	2	2	2
Casoid Bread	226·8	226·8	226·8	226·8	226·8	226·8	226·8	226·8	226·8	226·8	226·8
Almond Bread	226·8	226·8	226·8	226·8	226·8	226·8	226·8	226·8	226·8	226·8	226·8
Paget's milk	170	170	170	170	170	170	170	170	170	170	170
Mutton	113?		113	113?	170		198	113 ?	170	113	113
Beef				28		170					57
Chicken	57			57				57		57	
Ham		57					57				
Fish		85 ?	85 ?	85		85?				85 ?	
Cabbage	113	113	113	57	113			57	227	113	113
Brussels Sprouts						57	57				
Lettuce Watercress Mustard and Cress											
Celery											
Tomatoes			2								
Cheese	42	—	57			—			28	28	57
Bacon, rashers	1	—	—	—	1	—	1	1	2	—	1
Marmalade (Callard's)	+		+								
Custard (made with P.'s milk)											
Tea	+	+	+	+	+	+	+	+	+	+	+
Coffee or	+	ǂ	+	+	+	+	+	+	+	+	+
Cocoa	0	+	0	0	0	+	0	0	+	0	+
Hp. A.											
Spinach											
Sardines					5						
Margarine	About 156 grm. each day in place of butter										
Cream											
Jelly	568	568	284	568	568	568	568	568	284	—	—
Potatoes	28	28	28	28	28	28	28	28	28	28	28
Apples	156	156	156	156	156	156	312	156	—	156	156
Pheasant											
Milk (sour)											
Twitching	0	0	0	0	0	0	0	0	0	0	0
Thirst	0	+	0	0	0	+	0	0	0	0	0
Total urine c.c.	2,420	2,900	3,010	2,880		2,200	2,060	1,840	2,270	2,375	1,820
Total sugar grm.	89·47	119·31	101·56	99·60		80·28	73·42	60·00	62·08	59·78	58·40
Total nitrogen grm.	22·90	26·07	25·96	27·05		25·16	23·59	20·14	24·57	25·87	20·03
Total B-oxy. grm. Rotation	21·27	19·36	22·02	21·06		14·66	12·81	14·84	15·06	12·34	12·21

DECEMBER, 1909.

	11	12	13	14	15	16	17	18	19	20	21
Eggs	1	2	2	2	3	1	2	1	2	2	3
Casoid Bread	226·8	226·8	226·8	226·8	226·8	—	226·8	226·8	226·8	226·8	226·8
Almond Bread	226·8	226·8	226·8	226·8	226·8	453·6	226·8	226·8	226·8	226·8	226·8
Paget's milk	170	170	170	—	170	170	170	170	170	170	170 ?
Mutton	113	113 ?	226	--	113	226	85	113	--	113	—
Beef		113		57	57		85	28	113	85	57
Chicken	57								85		
Ham			57								
Fish	57				85	85	28	28			85 ?
Cabbage	113	57	113	57	85	113	85	57			
Brussels Sprouts											
Lettuce								+	+		
Watercress											
Mustard and Cress											
Celery											
Tomatoes							1	2	3		1
Cheese		57	28	14	28		28		28	28	28
Bacon, rashers	—	1	2	2	—	—	1	—	1	1	1
Marmalade (Callard's)						+ +		+			
Custard (made with P.'s milk)											
Tea	+	+	+	+	+	+	+	+	+	+	
Coffee or	+	+	+	—	+	+	+	+	+	+	
Cocoa	0	+	0	+	0	+	+	0	+	+	+
Hp. A.											
Spinach										57	
Sardines	6										
Margarine	About 157 grm. each day in place of butter.										
Cream										+	+
Jelly	—	—	—	—	—	—	—	—	—	—	
Potatoes	28	28	28	28	28	28	28	14	28	28	
Apples	156	156	312	312	—	312	312	312	312	468	312
Pheasant				113							
Milk (sour)				170							
Twitching	0	+	0	+	+	0	0	0	0	0	0
Thirst	0	0	0	0	0	0	0	0	0	0	0
Total urine c.c.		2,250	2,520	2,130	2,310		1,900		1,380	1,420	
Total sugar grm.		62·60	74·66	69·70	60·66		73·94		61·81	65·49	
Total nitrogen grm.		23·12	23·85	21·53	25·65		22·03		16·79	19·20	
Total B-oxy. grm. Rotation		20·15	20·06	15·83	14·94		6·54		4·23	3·50	

Case II. E. E. Laundress. Aged 21. Emaciated. Much thirst. Large appetite. Often constipated. Mother is hysterical. Brother stammers.

Admitted to the hospital 3/xi/9. Placed on a weighed diet 5/ii. This diet is given in the tables— all the quantities which relate to the food are in ounces ; but at the foot of the table the value of the food in terms of carbohydrate, nitrogen, and fat is given in grams. A comparison of the nitrogen of the food with that of the urine shows either that on many days the woman did not eat all the food weighed out for her, or that a part of the food was unabsorbed. It would not be surprising if the latter circumstance accounted, at all events in part, for most of the discrepancy, because the food was rich in fat. An examination of the faeces would have helped to decide this point, but I was unable to undertake such an examination.

This patient was frequently constipated : no stool was passed on the following days :

ii/7, 8, 9, 12, 13, 16, 19, 26, 27.
iii/1, 2, 3, 4, 16, 17, 18, 24, 25, 27, 28, 30.
iv/2, 3, 5, 13, 15, 17, 18, 20, 22, 26, 27, 29.
v/3, 5, 6, 7, 9, 11.

Her weight increased slightly at first, then became very steady. On 4/ii it was 5 st. 9 lb. (35·73 kilos): 26/ii 6 st. 0 lb. (38·1 kilos): 5/iii 6 st. 2 lb.: 9/iv 6 st. 4 lb.: 7/v 6 st. 2 lb.

The tables give the volume of the urine, the sugar as determined by rotation, the total nitrogen, and the hydroxybutyric acid as determined both by the polarimeter and by titration of the same extract as that used for polarization. The sugar was often determined by reduction, but the differences call for no remark ; they were of the usual order.

In the curve the sugar, nitrogen, and oxybutyric acid are plotted exactly in the same manner as for Case I ; the carbohydrate, nitrogen, and fat of the food are all plotted at one-tenth of their proper amount.

In the following table the salad is taken as 2 oz. and calculated as ' greens ': a tomato is taken as weighing 1·5 oz. and is also calculated as 'greens '. The brandy is not plotted on this curve nor reckoned in terms of carbohydrate, fat, and protein. The figures opposite articles of food marked with an asterisk are from analyses of my own. The ward sister, who was responsible for the diet, sent to me portions precisely like those on the patient's plate for analysis. No doubt there are inaccuracies in the total carbohydrate, nitrogen, and fat figures, for the meat would not always be equally fat, for instance, the sardines would not always have the same amount of adhering oil, and so on. But I believe, thanks to the sister, that the greatest possible care was taken.

E. E. took 4 grm. of sodium bicarbonate every day from her admission to 18/iii, when she took daily 8 grm. On 11/v signs of coma appeared (she had vomited the night before), and in the afternoon one pint of alkaline saline was given and retained, but the coma deepened. On 12/v she vomited again, and vomit and breath had a strong smell of acetone. She was able to retain brandy and water. A pint of alkaline saline was given every two hours, but in the evening this was not retained and its administration was discontinued. She died at 9 p.m.

On 21, 23, 25, 27/iv E. E. received 5 grm. of sodium hexosephosphate. This was prepared by Dr. Harden and Mr. Young. After the first two doses there was a diminution of the oxybutyric acid, but after the last two the acid was very high. It must be said that the new compound had not a fair trial in this case, for the patient did not like it, indeed she objected to it.

The post-mortem showed the patient to be suffering from tubercular bronchial pneumonia and from fatty degeneration of the heart, liver, and kidneys.

E. E. Diet Table.   (N.B. 1 oz. = 28·35 grm.; fluid oz. = 28·4 c.c.)

	Percentages.			Grm. per oz.		
	Carbohydrate.	Nitrogen.	Fat.	Carbohydrate.	Nitrogen.	Fat.
Oatmeal	18·5	0·59	1·8	5·25	0·167	0·51
Custard*	3·5	0·86	5·2	0·99	0·244	1·47
White bread*	56·0	1·15	1·27	15·88	0·326	0·36
Casoid bread*	0·0	5·10	27·70	—	1·446	7·85
Hospital diabetic bread*	4·6	4·52	25·40	1·30	1·281	6·45
Diabetic biscuits	—	9·72	25·60	—	2·756	7·3
Paget's milk*	—	0·95	6·8	—	0·260	1·93
Meat*	—	5·50	8·2	—	1·559	2·32
Bacon*	—	0·90	46·1	—	0·255	13·07
Eggs	—	2·00	12·0	—	0·567	3·40
Sardines*	—	1·54	26·5	—	0·437	7·51
Fish	—	3·00	1·0	—	0·851	0·28
Greens*	2·7	0·45	—	0·76	0·128	—
Apple*	15·0	—	—	4·30	—	—
Jam	25·0	—	—	7·10	—	—
Cream*	—	—	—	0·40	0·064	13·20
Milk*	4·1	0·54	3·17	1·20	0·158	0·93
Butter*	—	—	84·0	—	—	28·31

* My own analyses.

FEBRUARY, 1910.

	5	6	7	8	9	10	11	12	13
Bread	6	5	4	3	2	1	1	1	1
Butter	1	1	1½	2	2	1	½	½	1½
Meat	6	3¾	6	6	6	6	Fish 6	6	6
Greens	4	4	4	4	4	4	4	4	4
Bacon	2½	4	4	4	4	—	6½	2½	4
Eggs	1	1	1	1	1	1	1	1	1
Tea	40	35	58	40	40	40	40	40	40
Milk	72	56	66	46	51	66	40½	55	55
Water	43	42	29	34	44	34	25	25	34
C. Bread			3	6½	8½	6	1½	4½	7½
Sardines						2	2	—	2
Total urine c.c.		2,980	3,500	3,150	3,520	3,000			3,700
Total sugar grm.		205·38	182·49	173·50	157·44	142·63			172·90
Total nitrogen grm.		18·69	19·85	22·14	23·70	22·09			23·72
Total B-oxy. grm. Rotation		15·07	20·82	24·29	34·15	29·78			24·39
Titration		16·93	22·01	26·05	36·33	32·15			27·52
Diet.									
Carbohydrate	184·7	149·6	145·7	105·8	95·9	98·1	78·9	84·9	84·9
Nitrogen	24·9	18·9	28·0	29·6	33·0	31·3	19·6	27·1	32·7
Fat	146·1	145·2	194·8	215·2	235·1	168·1	178·8	151·9	233·9

FEBRUARY.

	14	15	16	17	18	19	20	21	22
Bread	1	1	1	1	1	—	—	—	—
Butter	2½	2½	2	2½	2½	2½	1½	1½	2½
Meat	6	6	6	6	Fish 8	6	6	6	6
Greens	4	4	4	4	—	4	4	4	4
Bacon	4	4	4	4	4	4	4	4	2½
Eggs	1	1	1	1	1	1	1	1	1
Tea	40	40	40	40	40	40	40	40	40
Milk	51	55	40½	55	60	45	35	55	55
Water	34	31	25	25	45	36	20½	25	25
C. Bread	7	7	Special 8	7½	8	9	9	9	9½
Sardines	2	1½	1½	1	1	1	1½	1½	1½
Custard				4	10	9½	10	10½	9½
Total urine c.c.	2,820	3,110	2,460	2,820	3,440	3,760		2,820	2,600
Total sugar grm.	143·96	138·27	130·8	151·18	170·55	179·99		147·28	142·45
Total nitrogen grm.	21·08	24·99	19·73	24·36	28·61	28·64		25·31	22·20
Total B-oxy. grm. Rotation	24·78	27·33	21·93	20·23	16·15	26·58		20·34	15·84
Titration	26·85	30·75	24·40	22·34	19·35	28·84		22·34	19·08
Diet.									
Carbohydrate	80·1	84·9	78·9	88·9	97·8	66·4	54·9	79·4	78·4
Nitrogen	31·3	31·7	32·4	34·3	34·8	34·8	33·6	36·9	37·0
Fat	250·0	250·1	241·3	256·5	262·1	266·3	247·7	257·0	263·7

	FEBRUARY.						MARCH.
	23	24	25	26	27	28	1
Butter	2½	3½	3½	3½	3½	3½	3½
Meat	6	6	—	6	6	6	6
Greens	4	4	4	4	4	4	4
Bacon	4	4	4	4	4	4	4
Eggs	1	1	1	1	1	1	1
Tea	40	40	40	40	40	40	38
Milk	45	55	55	45	45	20	
Water	20	25	25	40	35	40	41
C. Bread	9	9	8	9	8	9½	9
Sardines	1½	1½	1½	1	2	1½	1
Fish			8				
Paget's milk						10	12
Total urine c.c.	2,640	3,160	3,400		2,420	2,720	2,510
Total sugar grm.	134·02	148·43	167·93		113·33	125·72	88·75
Total nitrogen grm.	24·69	23·89	28·42		23·45	24·98	23·54
Total B-oxy. grm. Rotation	17·40	27·51	18·75		15·95	19·85	22·58
Titration	18·71	30·60	22·01		17·44	23·17	24·43
Diet.							
Carbohydrate	57·0	69·0	69·0	57·0	57·0	27·0	3·0
Nitrogen	32·7	34·3	28·9	32·5	31·5	33·0	28·5
Fat	256·1	289·2	261·8	276·1	275·7	280·1	257·4

MARCH.

	2	3	4	5	6	7	8
Butter	3½	3½	3½	3½	3½	3½	3½
Meat	6	6	—	—	6	4	6
Greens	4	4	4	4	4	4	4
Bacon	4	4	4	4	4	3	4
Eggs	1	1	1	1	1	1	1
Tea	38	40	40	40	40	40	40
Milk							
Water	40	61	56	52	40½	43	51
D. Bread	9	9½	10	10	10	10	11
Sardines	1	1½	1	—	—	—	—
Fish	—	—	8	—	—	-	—
Paget's milk	12	11	11	10½	11	11	11
Custard	8½	8	9				
Total urine c.c.	2,920	2,900	3,060			2,600	2,540
Total sugar grm.	125·39	117·20	108·78		87·88	105·35	
Total nitrogen grm.	26·00	27·89	28·79		24·50	24·04	
Total B-oxy. grm.	19·67	19·16	19·22		17·46	19·21	
Rotation							
Titration	21·53	21·09	20·72		18·99	21·26	
Diet.							
Carbohydrate	11·4	10·9	11·9	3·0	3·0	3·0	3·0
Nitrogen	30·6	31·2	29·4	19·8	29·3	25·9	30·7
Fat	269·9	274·9	264·7	240·9	255·7	238·0	263·6

MARCH.

	9	10	11	12	13	14
Butter	3½	3½	3½	2½	1½	2½
Meat	6	6	—	6	6	6
Greens	4	4	4	4	4	4
Bacon	4	4	4	4	4	4
D. Bread	11	11	7	8	8½	10
Fish	—	—	8	—	—	—
Eggs	1	1	1	1	1	1
Paget's milk	11	7	7	8	8	8
Tea	40	40	36	38	40	40
Water	51	62	45	42	38	51
Sardines	—	1½	1	1½	1½	1½
Total urine c.c.	2,600	2,580	2,760		2,740	2,790
Total sugar grm.	87·38	77·17	73·50		82·34	78·54
Total nitrogen grm.	24·32	22·93	22·57		23·86	22·81
Total B-oxy. grm.	19·54	19·79	19·23		22·50	23·77
Rotation						
Titration	21·37	21·34	19·79		24·10	25·26
Diet.						
Carbohydrate	3·0	3·0	3·0	3·0	3·0	3·0
Nitrogen	30·7	30·4	21·8	27·6	28·3	30·5
Fat	263·6	267·2	220·3	231·4	211·5	247·1

MARCH.

	15	16	17	18	19
Butter	3½	3	2½	3½	3
Meat	—	6	6	—	6
Greens	4	4	4	4	4
Bacon	4	2	2	—	4½
D. Bread	10	8½	9½	7	10
Fish	8	—	—	8	—
Eggs	1	1	1	1	1
Paget's milk	9	10	12	12	13
Tea	38	40	40	40	40
Water	41	42	33	43	38
Sardines	1½	1½	1½	1½	1½
Total urine c.c.	2,580	2,480	2,370	1,700	
Total sugar grm.	96·11	90·49	75·60	60·35	
Total nitrogen grm.	25·46	21·21	18·99	13·90	
Total B-oxy. grm.	19·52	19·95	24·42	14·31	
Rotation Titration	20·86	22·28	25·99	15·16	
Diet.					
Carbohydrate	3·0	3·0	3·0	3·0	3·0
Nitrogen	26·9	37·0	29·0	22·3	30·6
Fat	251·5	215·3	215·2	181·5	265·5

MARCH.

	20	21	22	23	24	25	26	27	28	29
C. Bread	12½	—	—	13½	13¼	14¼	11	6½	8½	7¾
Butter	4	4	?	5½	4¾	3½	4	2½	3½	2¾
Meat	—	—	—	—	—	—	6	6	6	6
Fish	—	—	—	—	—	8	—	—	—	—
Eggs	—	—	—	—	—	1	1	1	1	1
Greens	8½	11	—	12	6	4	4	4	4	8
Salad	+	+	—	+	+	—	+	+	+	—
Tomatoes	1	1	—	1	1	1	—	—	—	—
Oatmeal	—	—	9½	—	—	—	—	—	—	—
Sardines	—	—	—	—	—	1	1	1	1½	—
Bacon	—	—	—	—	—	1¼	3½	4	3	5
Paget's milk	9	6½	4	13	4	13	11	11	13	13
Tea	40	27	35	33	52	38	40	40	38	45
Water	25	13	7	19	9	15	26	30	20	38
Lemonade	—	20	—	10	20	—	—	—	—	—
Brandy	2	2	2	2	2	—	—	—	—	—
Total urine c.c.		1,960	1,860	2,100	1,840	2,420				2,720
Total sugar grm.		60·85	84·60	78·04	50·85	77·06				78·64
Total nitrogen grm.		14·03	10·21	15·94	16·23	21·48				19·73
Total B-oxy. grm.		20·19	6·86	16·54	19·42	21·22				26·16
Rotation Titration		22·26	7·21	17·73	20 51	22·15				26·61
Diet.										
Carbohydrate	12·9	11·0	49·9	11·8	7·2	4·2	4·5	4·5	4·5	6·0
Nitrogen	22·6	3·6	2·4	24·9	12·9	33·7	31·3	24·9	28·3	28·0
Fat	210·7	107·7	107·7	262·0	179·7	254·7	276·5	200·0	234·1	241·1

	MARCH.		APRIL.							
	30	31	1	2	3	4	5	6	7	8
C. Bread	6¼	5¾	5¾	8	7	6⅓	6	9	5¼	—
Butter	1¾	2	3	3	3¼	3½	2½	4½	3¾	2½
Fish	—	--	8	—	—	—	—	—	—	—
Meat	6	6	—	6	4	6	6	—	—	—
Eggs	1	1	1	1	1	1	1	—	--	—
Greens	4	4	4	4	4	4	4	16	12	--
Salad	+	—	—	—	+	+	+	+	+	—
Tomatoes	—	1	1	1	1	1	1	1	1	—
Oatmeal	—	—	—	—	—	—	—	—	—	6
Sardines	1½	1½	1½	1½	1½	1½	1½	—	—	—
Bacon	3½	2¾	3¼	3¼	4	3½	4	—	—	—
Paget's milk	13	11	11	11	13	13	13	9	9	14
Water	36	28	37	36	30	40	19	11½	19	23
Tea	38	37	38	38	38	36	36	36	36	38
Lemonade	—	—	—	—	—	—	—	15	13	—
Brandy	—	—	—	—	—	—	—	1	2	1½
D. Biscuits	—	—	--	—	1½	½	—	½	½	5
Total urine c.c.	2,040	2,100	2,000		2,560	2,620	2,440	2,340	2,080	1,860
Total sugar grm.	56·61	67·26	65·40		88·22	59·34	60·37	61·11	35·57	81·28
Total nitrogen grm.	15·02	15·73	16·41		17·85	17·09	15·88	14·64	11·24	6·48
Total B-oxy. grm. Rotation	20·21	18·28	16·73		25·79	30·68	23·78	17·46	10·44	6·98
Titration	20·77	19·08	17·47		26·48	31·98	26·61	17·52	10·38	7·46
Diet										
Carbohydrate	4·5	4·2	4·2	4·2	5·7	5·7	4·5	14·8	11·8	31·5
Nitrogen	25·2	23·7	21·3	27·1	27·6	27·1	24·9	19·3	13·3	18·4
Fat	193·3	181·6	203·4	229·5	247·9	240·5	213·8	198·9	139·7	126·1

	APRIL.									
	9	10	11	12	13	14	15	16	17	18
H. D.										
Bread	6½	8¼	8½	5¼	7	6¼	6	5	8½	4½
Butter	3½	3¼	2½	1½	3½	2¾	3½	2½	2	2
Fish	—	—	—	—	—	—	8	—	—	—
Meat	—	—	6	6	6	6	—	6	6	6
Eggs	—	-	1	1	1	1	1	1	1	1
Greens	14½	7	4	4	4	4	4	4	4	4
Salad	+	+	+	+	+	+	+	+	+	—
Tomatoes	1	2	—	—	—	—	—	1	1	—
Oatmeal	—	—	—	—	—	—	—	—	—	—
Sardines	—	—	1½	1½	1½	1½	1½	1½	1½	1
Bacon	—	—	—	4	4	4	2½	4	4	4
Paget's milk	12	12	14	14	13	14	14	14	14	14
Water	24½	40	30	30	35	30	30	30	35	30
Tea	38	34	36	36	36	36	36	36	36	36
Lemonade	10	—	—	—	—	—	—	—	—	—
Brandy	2	2	—	—	—	—	—	—	—	—
D. Biscuits	—	—	—	—	—	—	—	—	—	—
Jam	—	—	—	—	3	2	2	2	2	—
Total urine c.c.	1,980	1,620	2,400	2,240	2,220	2,660	2,580	2,340	2,840	2,580
Total sugar grm.	43·64	42·38	64·73	41·73	75·33	83·44	80·21	77·40	97·73	63·40
Total nitrogen grm.	9·20	10·23	16·80	14·11	16·41	17·50	18·85		20·08	17·41
Total B-oxy. grm. Rotation	8·58	19·41	25·18	19·64	19·54	28·02	22·35		29·73	28·50
Titration	10·77	20·00	26·4	20·39	21·17	30·12	23·53		31·14	29·56
Diet.										
Carbohydrate	22·2	19·8	15·6	11·3	34·9	26·8	26·5	26·3	29·5	8·9
Nitrogen	13·8	15·3	26·4	23·3	25·3	24·6	22·3	23·1	26·3	21·8
Fat	148·4	159·7	173·0	180·6	237·6	216·8	254·0	202·8	207·0	183·8

APRIL.

	19	20	21	22	23	24	25	26	27	28
H. D.										
Bread	3	5	3⅕	4	4¼	2½	5	4	4	5
Butter	2	2¼	1½	2¼	3	2	2	2	2	2½
Fish	+	—	—	8	—	—	—	—	—	—
Meat	6	6	6	—	8	6	6	6	6	6
Eggs	1	1	1	1	1	1	1	1	1	1
Greens	4	4	4	4	4	4	4	4	4	4
Salad	—	+	+	—	—	—	+	—	—	—
Tomatoes	—	+	+	+	+	+	+	+	—	+
Oatmeal	—	—	—	—	—	—	—	—	—	—
Sardines	—	1¾	—	1½	1	1½	1	1½	—	1
Bacon	3½	4	4	2½	1½	—	4	4	4	2½
Paget's milk	14	14	14	14	14	14	14	14	12	12
Water	30	35	30	30	30	30	30	25	25	38
Tea	32	36	36	36	36	36	36	36	36	36
Lemonade	—	—	—	—	—	—	—	—	—	—
Brandy	—	—	—	—	—	—	—	—	-	—
Jam	—	—	—	—	—	—	—	—	—	—
Fruit	—	2	—	—	—	—	—	—	—	—
Total urine c.c.	1,860	2,100	1,860	2,120	2,300 +10⅔ of 24th		2,780	2,400	2,680	1,860
Total sugar grm.	42·13	56·72	47·34	64·21	61·45		59·29	43·34	47·22	43·29
Total nitrogen grm.	12·62	13·97	12·71	16·77	17·36		16·39	14·45	14·56	12·50
Total B-oxy. grm. Rotation	13·50	24·25	16·92	15·65	14·31		28·47	24·38	27·22	19·74
Titration	14·51	25·54	17·13	16·51	16·69		30·18	25·20	28·40	20·61
Diet.										
Carbohydrate	6·9	20·8	10·3	9·4	9·7	7·5	12·2	9·4	8·2	10·7
Nitrogen	26·1	23·2	20·6	18·7	24·2	18·6	22·9	21·6	20·2	21·7
Fat	162·3	198·7	158·0	159·1	178·0	122·4	187·1	184·4	169·3	175·6

	APRIL		MAY									
	29	30	1	2	3	4	5	6	7	8	9	10
Cream	—	—	3	—	—	—	—	—	—	3	2	2
H. D.												
Bread	$5\frac{1}{4}$	2	3	6	$5\frac{1}{2}$	6	6	$4\frac{1}{2}$	$6\frac{3}{4}$	2	3	—
Butter	2	2	2	3	3	3	2	$1\frac{3}{4}$	$4\frac{3}{4}$	$2\frac{1}{2}$	$2\frac{1}{2}$	—
Fish	14	—	8	—	4	—	—	8	11	—	5	—
Meat	—	6	—	4	6	1	$3\frac{3}{4}$	4	6	$3\frac{1}{2}$	6	—
Greens	4	4	4	4	4	$1\frac{1}{2}$	4	4	4	$3\frac{1}{2}$	$\frac{1}{2}$	—
Eggs	1	1	1	1	1	1	1	1	1	—	1	—
Salad	—	—	- -	—	—	—	—	—	—	—	—	—
Tomatoes	—	2	1	3	3	3	2	1	—	1	1	1
Oatmeal	—	—	$2\frac{1}{2}$	—	—	—	—	—	—	$2\frac{1}{2}$	2	2
Sardines	—	—	—	$\frac{1}{2}$	—	—	—	—	—	—	—	—
Bacon	4	—	$4\frac{1}{2}$	$3\frac{1}{2}$	3	$6\frac{1}{2}$	5	2	2	—	2	—
Paget's milk	14	12	12	14	12	14	14	14	14	9	13	7
Water	31	42	30	30	27	38	32	40	34	22	41	13
Tea	36	38	38	32	33	36	36	38	36	31	36	18
Lemonade	—	—	—	—	—	—	—	—	—	—	—	—
Brandy	—	—	—	—	—	—	—	—	—	—	—	6
Fruit	—	—	—	—	—	—	—	—	+	—	—	—
P. Biscuits	—	2	$\frac{1}{2}$	—	—	—	—	—	—	—	—	—
S. Water	—	—	—	—	—	—	—	—	—	6	—	5
Milk	—	—	—	—	—	—	—	—	—	—	—	12
Total urine c c.	2,800	1,620	3,320	1,980	2,390	2,440	2,300	2,980	1,340	2,340	2,760	1,490
Total sugar grm.	68·21	50·22	71·12	41·95	58·44	53·20	50·69	81·50	38·11	50·80	72·47	41·18
Total nitrogen grm.	17·21		19·10	12·19	15·79	12·81	12·59	19·11	8·22	13·40	13·10	7·11
Total B-oxy. grm. Rotation	22·52		25·94		20·66	22·86	19·69	17·42		17·70	21·40	
Titration	23·65		26·63	19·82	21·60	22·94	20·44	18·55		18·34	22·50	
Diet.												
Carbohydrate	9·8	7·9	22·4	14·3	13·7	12·4	13·1	9·7	11·8	20·7	16·7	26·8
Nitrogen	24·9	23·5	18·7	20·7	25·9	16·4	21·4	24·4	33·1	11·6	23·1	4·4
Fat	171·2	118·7	202·4	200·5	190·8	230·8	193·9	140·2	233·2	138·8	179·3	52·1

A study of the curve shows :

a. The extraordinary increase of the oxybutyric acid excretion on beginning to restrict the carbohydrate. By 9/xi, that is in six days, the acid had risen from nearly nothing to 34 grm. The total production of acid would be considerably more than this, for, as will appear later, in the severe cases of diabetes, acetoacetic acid accompanies the oxybutyric acid to the extent of one-third or more of the latter. Thus sudden provision has to be made for the removal or catabolism of highly abnormal amounts of two substances, both acids, and one of them quite a toxic substance—as will be seen later—as well. The acetoacetic
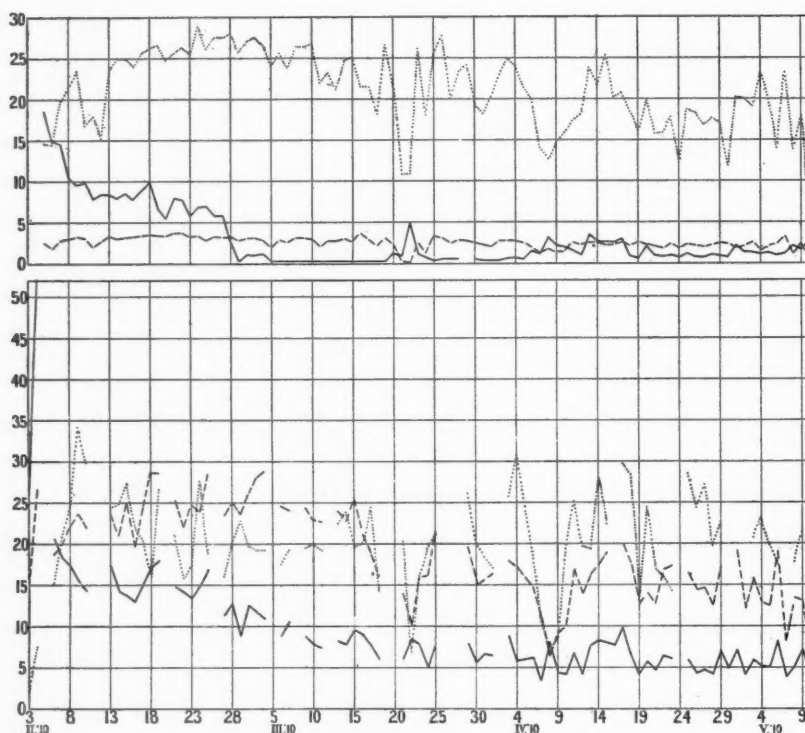
Curve II.   E. E.

acid, which is very probably the primary product, has to be provided with base, then in part reduced to oxybutyric acid, in part excreted, and in part resolved into acetone. Being a far stronger acid than carbonic or the monobasic phosphate, the bicarbonates and dibasic phosphates will give up base ; but the mass action of the latter will soon put a term to this process and base will have to be provided in the form of ammonia, and the latter will neutralize acetoacetic acid instead of forming urea, and glycocoll for hippuric formation. Of all these processes I should regard failure to reduce acetoacetic acid to oxybutyric acid as the most serious thing to happen. In that event there might

be a sufficient accumulation of this substance to produce coma. I suggest that it is in this way that coma is induced by the abrupt withdrawal of carbohydrate from the diet of a severe diabetic. The body requires time to adjust its processes to the altered conditions in this as in so many other cases. In this case the carbohydrate was reduced from 185 to 96 grm. in four days, that is at the rate of 22 grm. a day, yet it caused this excessive production of acid. Such a rate of reduction is evidently far too high in a case of this kind. The results of the trials of the von Noorden treatment show, however, that if the other items of the diet are reduced as well as the carbohydrate there is not the same production of acid ; and the same thing was observed long ago by those who advocated the interposition of one or more days of complete abstinence before changing from a carbohydrate to a non-carbohydrate or poor carbohydrate diet.

While the carbohydrate is being reduced it is a most desirable thing to know the amount of the acetoacetic acid, and, if possible, of the oxybutyric acid also, in order that the reduction may be arrested as soon as the quantity of the acids shows an upward tendency. This point is well illustrated by the cases of S. G. and W. H. R. Moreover, it is not advisable to continue the reduction beyond a certain limit, which is probably different for each case. A serious outbreak of acid production, such as that of J. H. B. and of this patient, is difficult to remedy, and I believe that it causes definite injury to the body, an injury which requires much time to repair. It is the same with many other kinds of poisoning, as for example, carbon monoxide poisoning.

The fact that once a high acid production has been brought about it is exceedingly difficult to get rid of it again was clearly shown long ago by Hirschfeld (36) ; but he only determined the ' acetone'. Thus the diabetic patient K., aged 30, weight 56 kilos, on the diets indicated excreted acetone as follows :

	14/vii/92.	22/vii.	26/vii.	27/vii.	30/vii.	1–3/viii.
Protein (grm.)	156	178	178	178	178	178
Fat (grm.)	190	195	195	195	195	195
Carbohydrate (grm.)	140	0	0	60	90	126
Acetone (mg.)	110	282	523	521	408	421

After four weeks on a diet nearly the same as that of 1–3/viii, the acetone had only fallen to 189 mg. He calls this a severe case, but as regards the acidosis it is a slight case. The writer is of the opinion that the total withdrawal of carbohydrate from a diet rich in protein and fat is an irremediable error.

b. That after the outbeak of acid formation resulting from restriction of the carbohydrate the oxybutyric acid curve passes on 17/ii to a position between the nitrogen and sugar curves ; but after 29/iii the acid curve is almost always well above the other two. This is the position of dangerous acid production. The acid curve had this position in the case of J. H. B. during the severe outbreak of acid formation which accompanied the reduction of carbohydrate in his case. From the curve it is seen that the intermediate position of the acid curve corresponds to a high nitrogen intake of about 36 grm. a day and a fairly

high output of sugar; and the outside position of this curve corresponds to a lower nitrogen intake of about 22 to 23 grm. a day and a lower output of sugar. These results are quite in accord with those obtained by Hirschfeld (37) for the excretion of 'acetone' by normal people when placed on a diet free or nearly so from carbohydrate, and respectively poor and rich in protein—except, of course, that the absolute magnitude of the 'acetone' figures are much lower than they are in the case of a diabetic. For example, on the eighth day of the diets indicated the acetone excretion was as follows:

	Case R.		Case L.		Case Kl.	
Protein (grm.)	77·5	133·4	106·8	179·2	110·0	172·0
Fat (grm.)	72·0	115·4	122·2	88·9	120·0	180·0
Acetone (mg.)	49·6	29·6	59·7	26·7	51·0	16·7

Hirschfeld states that while moderate amounts of protein increase the acetonuria large amounts actually diminish it.

This is the case with E. E. It is shown by the $D : N$ ratio:

Total urinary sugar on days available between 1/iii and 16/iii (13) . .	1218·9
„ food „ „ „ „ . .	64·2
	1154·7
Total urinary nitrogen	317·9
∴ $D : N = 3·6$.	
Total urinary sugar on days available between 11/iv and 4/v (21) . .	1264·3
„ food „ „ „ „ . .	323·7
	940·6
Total urinary nitrogen	329·8
∴ $D : N = 2·85$.	

Now the food sugar is probably too high in the second period. To correct for this we may assume that of the food nitrogen 1 grm. per day is excreted in the faeces. Deducting this we have $(475·8 - 21) = 454·8$ grm., of which only 329·8 appeared in the urine, i. e. 72·5 per cent. We will suppose that the food sugar is reduced by this amount so that it becomes 234·7 grm. Then $D : N = 3·1$. Thus in this case in the first period we have on the higher protein, higher fat, and lower carbohydrate diet more sugar produced from 1 grm. of nitrogen and a lower excretion of oxybutyric acid than in the second period. It is very interesting to observe the lower excretion of oxybutyric acid on the higher fat diet. (20·1 grm. a day against 22·5 is the average.)

On 21 and 22/iii a modified von Noorden treatment was attempted—only butter, vegetables, and Paget's milk being given on 21/iii, and the same with the addition of oatmeal porridge on 22/iii. As is seen from the curve there was a great fall in the nitrogen and oxybutyric acid excretions and a small rise in the sugar. Immediately afterwards the values return to what they were before the treatment. A very similar treatment with the like result was adopted on 8 and 9/iv. Better examples of the von Noorden treatment will be found below.

Case III. S. G. Coal-carman.   Aged 27.

Admitted 9/xii/11. He noticed in August that he had become thirsty, thin, and weak, and that he became breathless after exertion. There was no history of diabetes in the family : his father was alive and well : his mother was dead : he had three brothers all alive and well.

His organs were practically normal.

His weight was very steady ; its variations were :

9/xii/11, 8 st. 5 lb. : 19/xii/11, 8 st. 4 lb. : 23/xii/11, 8 st. 8 lb. : 6/i/12, 8 st. 7 lb. : 9/ii/12, 8 st. 8 lb. : 23/ii/12, 8 st. 12 lb. : 10/iii/12, 9 st. : 24/iii/12, 8 st. 9 lb.

No stool was passed on the following days :

xii/11.   16, 18, 20, 22, 26, 28, 30.

i/12.   2, 5, 7, 12, 19, 27.   Also 9/ii and 26/iii.

Starting 17/xii/11 he received daily 2 grm. of sodium bicarbonate till 24/i/12, when he took daily 4 grm. sodium bicarbonate and 1·5 grm. of potassium citrate three times a day.

The diet of this patient is given in the following table :

	Percentages.			Grm. per oz.		
	Carbo-hydrate.	Nitrogen.	Fat.	Carbo-hydrate.	Nitrogen.	Fat.
White Bread	55·9	1·15	1·27	15·88	0·33	0·36
Diabetic Bread	4·59	4·13	30·06	1·30	1·17	8·53
Butter	—	—	84·28	—	—	23·81
Meat	—	5·50	8·20	—	1·56	2·32
Custard	3·50	0·86	5·20	0·99	0·24	1·47
Eggs	—	2·00	12·00	—	—	—
Bacon	—	0·90	46·10	—	0·26	13·07
Sardines	—	3·045	20·28	—	0·85	5·70
Milk	3·50	0·54	3·20	0·99	0·154	0·91
Fish	2·00	·50	0·50	0·57	0·99	0·14
Greens	2·69	0·452	—	0·76	0·13	—
Lemco	—	2·64	—	—	0·748	—
Cheese	—	4·09	33·53	—	1·16	9·50
Potato	17·04	0·26	—	4·82	0·07	—

Except for the eggs and fish all the analyses are my own. Foods such as meat, potato, greens, were analysed just as they were given to the patient; the samples taken were given to me as quite typical of those eaten every day by the patient. They cannot, of course, be quite accurate, for the greens and potatoes would not always be equally well drained nor would every sample of bacon be equally fat. The Lemco is not added in before 10/ii/12.

As regards the urinary analyses the sugar was determined always by rotation and, with very few exceptions, by reduction also—only the figures for the rotation are given. The oxybutyric acid was always determined both by rotation and titration, only the former being given. The acidity is given for the total day's urine in terms of normal acid: it was determined by titration with standard caustic soda and phenolphthalein as indicator. On account of the pale colour of the urine there was no difficulty with the end point.

Occasionally two days' urine were mixed and analysed together and the mean results taken for each of the days. Such results are bracketed in the tables and are easily seen on the curves. This was very unfortunate on 23 and 24/xii, for no doubt the figures for 23/xii were very different from those of the following day.

There is often a considerable discrepancy between the nitrogen of the food and that of the urine, and no doubt on a rich protein diet such as this more nitrogen is excreted in the faeces than on the usual diet. The patient ate his

food well and is only recorded as having failed to eat his breakfast on 16/ii/12, and this appears to be shown by the large decrease in the oxybutyric acid and by the smaller decreases in sugar and nitrogen.

It will be seen from the curve that on the first three days there was no oxybutyric acid in the urine. On 13/xii reduction of the white bread was begun and diabetic bread was substituted for it. The patient liked the diabetic bread and ate it freely. As the oxybutyric acid increased very rapidly with the diminution of the white bread a pause was made in the reduction on 17/xii; but the increase of acid continued for four days longer. There is no doubt that if the reduction of carbohydrate had continued the state of this patient would have been precarious in the extreme, and the curve would have assumed the type shown by J. H. B. at the beginning of his treatment and of that shown by E. E. before the fatal coma set in. After this subsidence of the acid excretion the patient's condition remained very satisfactory, and the acid showed a very slow decline which would no doubt have continued. It will be remembered that Hirschfeld's case, quoted above, took four weeks to make a partial recovery from a far less serious outbreak of acid production than this. The conclusion that a severe outbreak of acidosis inflicts an injury upon the organism from which it recovers with difficulty appears to be irresistible. That S. G. ate so freely of diabetic bread of his own free will may be due to an instinct prompting him to remedy in that way the sense of discomfort caused by the rapidly increasing acid production; for, as we have seen, large amounts of protein have the property of suppressing acidosis. At this time the importance of the time factor in effecting changes in the diet of a diabetic was not fully realized, and a further attempt was made to restrict the carbohydrate. This began on 20/i/12, when the white bread was attacked again, and, as it was thought, very cautiously. The response was immediate—and except for a fall on 28/i/12, which, I believe, was due to a loss of urine—the oxybutyric soars uncontrollably, and remains very high indeed this time for five days after the disappearance of the white bread. After this outbreak it is much more difficult to bring the acid within reasonable limits again : an attempt was made to do this by starting on 7/ii/12 with 2 oz. of potato, reaching 6 oz. on 15/ii and keeping afterwards at 5 oz. The amount of carbohydrate from this time onward, namely about 100 grm., was not quite sufficient to enable the patient to deal with the liberal supply of protein and fat in the food. The excretion of oxybutyric acid is very gradually falling, and no doubt with about 130 grm. of sugar the fall would have been more rapid.

The D : N ratio in this case between 7/i/12 and 19/i/12, neglecting 12/i/12 where there was a loss of urine, averages 4·22 for the twelve days.

For the period 3/ii/12 to 18/ii/12, omitting 6/ii/12 when the nitrogen was lost, we have as the average of fifteen days D : N = 4·04. Correcting these figures as in the case of E. E., but allowing 1·5 grm. N in the faeces on account of the richer diet, we obtain for these two periods 5·3 and 4·5 respectively.

Here again on the richer protein diet we have more sugar produced per gram of nitrogen and a lower output of oxybutyric acid (13·8 and 26 gr. respectively for the daily average). The great difference in the output of acid during the two periods is, of course, mainly due to the richer carbohydrate diet of the first period.

It is worth while pointing out that the increase of oxybutyric acid during the period 21/i/12 to 26/i/12 is accompanied by a decrease of fat in the diet and an increase of nitrogen. As regards the acidity of this urine the figures show a very fair parallelism with the amount of oxybutyric acid present in the urine. Thus, on 11/xii/11 the acidity is 69 with no oxybutyric acid, and on 21/xii/11 it is 181 with 26·7 grm. of the acid, and on 9/ii/12 the highest acidity 193 coincides with the highest value of the oxbutyric acid 39·6 grm. The fact than an acidity of 69 c.c. N. acid was observed when no oxybutyric acid could be found in 500 c.c. of the urine after 72 hours' extraction with ether

shows that a considerable proportion of the acidity of a diabetic urine is due to other acids than oxybutyric. Even in the most acid urines hippuric, benzoic, and acetoacetic acids are almost completely united to bases (see p. 389); but uric, carbonic, and sodium dihydrogen phosphate are almost entirely free. (Sodium dihydrogen phosphate acts as a weak acid because it produces hydrogen ions in accordance with the equations:

$$NaH_2PO_4 = \overset{+}{Na} + H_2\overset{-}{P}O_4$$
$$H_2PO_4 = \overset{+}{H} + H\overset{=}{P}O_4.)$$
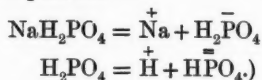
Of these three acids the two first are present in far smaller amount than the last, so that we may assume the acidity of $11/xii/11$ was due almost entirely to acid sodium phosphate; unfortunately I have only an accurate determination of the phosphoric acid on one day. On $3/iii/12$ S. G. excreted 5·018 gr. P_2O_5. If all this phosphoric oxide was present as NaH_2PO_4, then since the latter reacts as a monobasic acid to phenolphthalein the acidity due to it would be equal to 70·7 c.c. N. acid. The total acidity on this day was 119 c.c. N. acid; and we may assume without any great error that the difference $(119-70·7) = 38·3$ c.c. was due to free oxybutyric acid. Now 38·3 c.c. N. acid = 3·98 gr. of the acid, which would give 26 per cent. of the acid present in the free state. This agrees fairly well with the figure calculated from Henderson's formula for the amount of free oxybutyric acid in a urine whose acidity is equal to a hydrogen ion concentration of 1×10^{-5}, namely 33·3 per cent. (see p. 389). If we may assume the same amount of phosphoric acid to be present on $21/xii/11$ and $9/ii/12$—and on a rich diet such as this we shall not be far wrong in doing so—the percentages of free acid would be 43 and 32 respectively.

Acting on a suggestion of Major F. H. Foulkes, F.R.C.S., I.M.S., this patient was given glucose per rectum as shown on the table of diet. Foulkes thought (a) that the diabetic was quite able to metabolize sugar; (b) that he was unable to absorb this substance from the upper part of the intestinal tract and that consequently it was destroyed by fermentation before reaching the lower bowel; (c) that the diabetic could absorb sugar from the lower bowel and utilize it. He had found sugar administered in this way to diabetic patients in India to produce very beneficial results. As is seen from the curves, the sugar so administered does not appear to produce any marked effect.

S. G. was also given considerable amounts of extract of meat ('Lemco'); and this was without visible effect except that it caused a small rise of nitrogen.

When the urinary analyses ceased the patient's weight was 8 st. 12 lb.: the weighed diet ceased $13/iii/12$. His weight on $10/iii/12$ was 9 st. and on $24/iii/12$ it was 8 st. 9 lb. The patient was discharged in better condition than when he entered. But, speaking from the appearance of the curves, the condition of S. G. was never so good after $19/i/12$ when the second attempt to reduce his carbohydrate was made. This case seems to show that on a rich protein fat diet about 120 grm. of carbohydrate are required to keep acid formation at a minimum.

Pavy, in his book on *Carbohydrate Metabolism and Diabetes*, 1906, p. 120, has the following statement: ' If there is no diaceturia existing when the patient falls under observation for treatment I do not consider there is the slightest risk incurred in passing at once to the fully restricted diet for diabetes. . . . I have never seen any ill effect from it.'

I believe this case and also Case II demonstrate the inadvisability of such a procedure as the one suggested by Pavy—in the only way in which it can be demonstrated—that is, by numbers obtained in the course of a prolonged observation of cases.
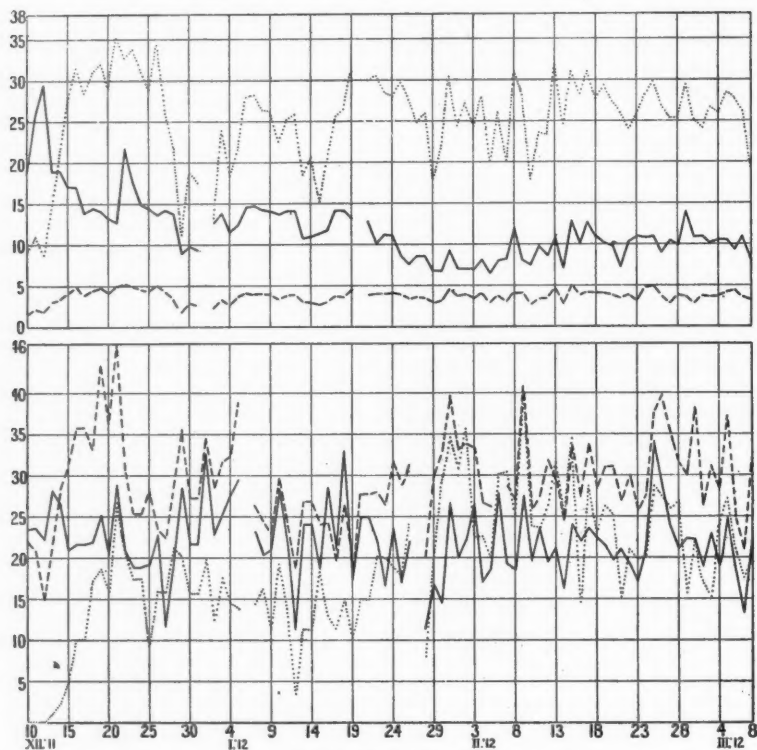
Curve III   Case S. G.

DECEMBER, 1911.

	9	10	11	12	13	14	15	16	17	18	19	20	21
White Bread	11	10	14	17	9	8	6	6	4	4	4	4	4
Diabetic Bread	—	—	—	—	5	12	21	23	16	18	22	17	26
Butter	2	2	2	2	2	2	2	2	2	2	2	2	2
Meat	6	4	6	5	6	6	—	6	4	6	—	6	6
Custard	—	9	19	7	7	7	6	7	7	8	7	7	7
Eggs	—	—	—	—	—	—	—	2	2	2	2	2	2
Bacon	—	—	—	—	—	—	—	—	2	2	2	2	2
Sardines	—	—	—	—	—	—	—	—	—	—	—	—	—
Milk	7	20	16	14	28	36	38	34	44	46	36	36	18
Fish	—	—	—	—	—	—	8	—	—	—	10	—	—
Greens	4	3	—	6	6	6	—	6	6	6	—	6	6
Tea	48	37	30	36	36	64	60	70	70	70	60	70	66
Lemonade	10	10	8	50	10	—	—	30	40	40	40	10	18
Water													
Total urine c.c.		2,750	2,730	2,390	3,270	3,500	3,240	3,460	3,460	3,610	4,490	3,700	5,160
Total sugar grm.		233·6	236·3	222·8	282·4	265·1	209·5	215·9	215·9	218·3	252·0	203·1	287·9
Total nitrogen grm.		21·9	20·6	14·8	21·7	28·4	31·3	35·7	35·7	33·1	43·4	36·3	45·8
Total oxy-butyric grm.		—	—	—	0·8	2·3	6·2	10·0	10·0	17·2	18·6	15·8	26·7
Total acidity c.c. N. acid		—	—	69	95	—	—	—	—	132	166	133	181
Diet.													
Carbohydrate grm.	184·7	189·9	257·0	295·3	188·6	189·8	170·7	170·3	139·4	144·9	140·4	132·8	126·6
Nitrogen grm.	14·6	15·3	21·2	18·1	30·2	34·1	41·8	48·2	38·3	44·3	46·9	41·3	49·1
Fat grm.	71·9	91·9	109·1	88·4	143·2	209·8	274·2	314·9	284·3	309·3	320·3	290·2	350·5

	DECEMBER, 1911.										JANUARY, 1912.		
	22	23	24	25	26	27	28	29	30	31	1	2	3
White Bread	4	4	4	4	4	4	4	4	4	4		4	4
Diabetic Bread	18	18	18	15	22	14	9	—	9	8		—	10
Butter	2	2	2	2	2	2	2	2	2	2		2	2
Meat	5	6	6	7	7	7	6	6	6	6		6	4
Custard	6	7	7	8	8	6	7	7	8	7		8	8
Eggs	2	2	2	2	2	4	2	2	2	2		—	2
Bacon	2	2	2	1	2	—	1	1	1	1		—	1·5
Sardines	—	—	—	2	2	2	—	—	—	—		—	1
Milk	70	78	50	50	30	50	50	15	10	10		50	50
Fish	6	—	—	--	—	—	—	—	—	—		—	—
Greens	6	6	8	6	8	8	8	6	6	6		6	5
Tea	70	70	70	70	70	40	50	80	80	80		50	50
Lemonade	40	35	60	40	30	40	40	10	—	10		40	20
Water	—	—	—	—	30	30	30	—	20	20		30	30
Glucose per rectum	—	—	—	—	—	—	—	—	—	—		—	1·5
Total urine c.c.	3,860	3,275	3,275	4,970	3,830	2,760	3,820	4,660	3,510	3,510	4,820	4,090	4,110
Total sugar grm.	207·5	188·1	188·1	191·7	227·7	116·4	191·6	285·3	215·9	215·9	324·8	227·7	252·4
Total nitrogen grm.	30·7	25·3	25·3	28·2	23·5	22·5	28·5	35·6	27·3	27·3	34·5	28·5	31·6
Total oxy-butyric grm.	20·5	17·4	17·4	9·3	15·9	15·9	21·1	20·1	15·7	15·7	19·8	12·4	17·6
Total acidity c.c. N. acid	128	113	113	119	107	123	152	184	134	134	158	120	144
Diet.													
Carbohydrate grm.	217·3	175·6	149·4	145·0	135·8	143·2	136·7	88·9	97·6	94·3		125·5	137·7
Nitrogen grm.	51·9	49·0	44·9	44·4	50·0	42·7	33·9	17·7	28·0	26·3		23·3	33·0
Fat grm.	326·7	336·9	311·4	287·9	342·5	263·4	220·1	111·5	186·7	175·2		133·2	239·2

JANUARY, 1912.

	4	5	6	7	8	9	10	11	12	13	14	15	16
White Bread	4	4	4	4	4	4	4	4	4	4	4	4	4
Diabetic Bread	8	11·5	14	14	12	11	8	11·5	11·5	8	9	5·5	8
Butter	2	2	2	2	2	2	2	2	2	2	2	2	2
Meat	4	6	6	4	6	6	6	6	6	6	6	6	6
Custard	8	9	9	10	10	10	9	9	9	9	9	9	9
Eggs	2	2	2	2	2	2	2	2	2	2	—	—	2
Bacon	—	—	1·5	1·5	1·5	2	1·5	1·5	1·5	—	2	—	1·5
Sardines	1	—	1	2	1	1	0·5	—	1	1·5	1·5	2	—
Milk	30	35	50	50	50	50	50	50	50	20	20	50	50
Fish	—	—	—	—	—	—	—	—	—	—	—	—	—
Greens	4	4	6	6	6	4	6	6	6	6	6	6	6
Tea	50	50	50	50	50	50	50	50	50	50	50	50	50
Lemonade	20	30	—	—	20	30	30	30	30	30	30	30	20
Water	20	10	40	40	20	20	40	20	20	20	20	20	20
Glucose per rectum	—	—	—	—	1·5	1·5	1·5	1·5	1·5	1·5	1·5	0·5	0·5
Lemco	—	—	—	—	—	—	—	—	—	—	—	—	—
Total urine c.c.	4,360	5,040	—	3,960	3,180	3,400	4,310	3,360	2,190	3,480	3,480	3,170	4,000
Total sugar grm.	274·5	295·2	—	232·8	203·1	211·1	283·9	218·2	114·1	239·1	239·1	185·7	283·2
Total nitrogen grm.	32·4	38·8	—	26·3	24·5	22·9	306	25·3	18·6	26·7	26·7	24·0	24·2
Total oxy-butyric grm.	14·5	13·8	—	14·4	16·0	11·4	19·1	13·7	3·5	11·3	11·3	18·3	12·8
Total acidity c.c. N. acid	152	151	—	118	137	106	144	122	71	112	112	113	104
Diet.													
Carbohydrate grm.	114·6	125·1	144·7	145·7	143·1	140·3	136·9	141·4	141·4	107·2	108·5	112·5	117·1
Nitrogen grm.	27·1	34·5	41·2	39·2	39·1	37·8	33·8	37·4	38·3	29·6	29·1	26·4	30·3
Fat grm.	184·3	219·1	279·4	281·9	263·8	261·8	225·3	252·4	258·1	184·2	205·9	153·3	204·3

(Fragmentary figures visible in the left margin, partly cut off): 21, 4, 26, 2, 6, 7, 2, 2, 18, 6, 66, 18, 5,160, 287·9, 45·8, 26·7, 181, 126·6, 49·1, 350·5

JANUARY, 1912.

	17	18	19	20	21	22	23	24	25	26	27	28	29
White Bread	4	4	4	3·5	3	2·5	2	2	1·5	1	1·5	—	—
Diabetic Bread	10·5	12	18	5+	13	15	13	12	14	14	13	9	4
Butter	2	2	2	2	2	2	2	2	2	2	2	2	2
Meat	6	4	7	6	6	6	6	7	6	—	6	6	6
Custard	9	10	10	9	9	9	9	9	10	6	10	9	10
Eggs	2	2	2	2	—	2	2	2	2	2	2	2	2
Bacon	2	1·5	2	2	4·5	4	2·5	2·5	4	4	1·5	3	—
Sardines	1	2	2	—	1·5	1·5	1·5	1·5	1·5	1	—	—	2
Milk	50	50	30	50	50	30	50	50	30	30	30	60	50
Fish	—	—	—	—	—	—	—	—	—	7	—	—	—
Greens	6	3	6	6	6	6	6	6	6	3	6	6	6
Tea	50	50	50	50	50	50	50	50	50	50	50	50	50
Lemonade	20	10	20	20	20	30	30	30	20	20	20	20	10
Water	20	30	20	20	20	20	20	20	20	20	10	25	50
Glucose per rectum	0·5	—	—	—	—	—	—	—	—	—	—	—	—
Lemco	—	—	—	—	—	0·5	1·5	1	1	1	1	1	1
Total urine c.c.	3,010	4,980	2,660	3,765	3,765	3,540	3,530	4,120	3,430	4,080		1,980	3,470
Total sugar grm.	210·0	329·5	175·0	249·9	249·9	220·1	165·3	236·3	169·8	218·5		115·4	166·8
Total nitrogen grm.	19·7	26·2	18·6	27·7	27·7	28·0	26·4	31·7	28·8	31·3		20·0	29·6
Total oxy-butyric grm.	11·5	14·9	10·4	15·1	15·1	20·1	19·9	18·8	17·8	24·0		8·1	20·9
Total acidity c.c. N. acid	84	136	87	107	107	120	134	175	134	142		80	104
Diet.													
Carbohydrate grm.	140·1	140·8	131·1	118·6	127·5	102·4	111·6	110·3	86·2	76·0	84·9	84·6	69·2
Nitrogen grm.	37·2	36·4	45·5	24·0	38·8	39·9	40·1	40·5	38·6	34·3	35·5	35·1	28·9
Fat grm.	256·1	264·9	311·4	160·6	299·6	304·7	286·1	279·9	297·3	275·5	247·5	258·3	180·2

JANUARY, 1912.   FEBRUARY, 1912.

	30	31	1	2	3	4	5	6	7	8	9	10	11
White Bread	—	—	—	—	—	—	—	—	—	—	—	—	—
Diabetic Bread	7	15	14	16	12	15·5	7	13	7	17	11	3	10
Butter	2	2	2	2	2	2	2	2	2	2	2	2	2
Meat	6	6	6	6	6	6	6	6	6	6	9	6	4
Custard	9	10	9	8	8	8	8	9	9	9	8	8	8
Eggs	2	2	2	2	2	2	2	2	2	2	2	2	2
Bacon	1·5	1·5	—	1	1	1	1	1·5	1	3·5	3·5	2	1
Sardines	2	2	—	—	—	—	—	—	—	2	—	—	—
Milk	45	60	40	40	45	50	45	50	50	35	40	45	60
Fish	—	—	—	—	—	—	—	—	—	—	—	—	—
Greens	6	6	6	4	4	4	4	6	6	6	6	6	3
Tea	50	50	50	50	50	50	50	50	50	55	50	50	50
Lemonade	—	10	10	30	—	20	10	10	10	20	20	10	—
Water	45	60	40	40	45	25	30	20	20	15	20	20	20
Lemco	1	1	—	—	—	—	—	—	—	—	—	1·8	1·8
Potato	—	—	—	—	—	—	—	—	2	2	3	3	3
Cheese	—	—	—	—	—	—	—	—	—	—	—	—	—
Total urine c.c.	3,730	5,590	4,360	4,600	4,640	3,190	3,760	4,890	3,810	3,510	5,520	3,420	3,940
Total sugar grm.	144·6	286·2	200·0	221·1	263·5	170·0	186·8	278·1	193·2	185·0	274·7	196·1	238·6
Total nitrogen grm.	32·9	39·7	33·2	33·8	33·5	26·6	26·2	—	28·7	26·9	40·6	26·1	27·4
Total oxy-butyric grm.	29·4	34·5	30·9	35·5	22·5	22·5	20·1	30·1	30·3	25·2	39·6	23·8	23·7
Total acidity c.c. N. acid	147	182	175	—	151	114	115	147	137	121	193	131	112
Diet.													
Carbohydrate grm.	67·1	93·4	71·3	71·4	71·1	80·6	64·6	79·9	81·7	121·3	80·8	75·4	97·1
Nitrogen grm.	31·8	43·7	37·1	39·2	35·3	40·2	29·4	37·1	30·1	40·9	40·9	26·5	33·2
Fat grm.	219·4	302·8	243·6	272·2	242·7	277·1	200·0	259·2	201·5	310·3	280·6	179·0	234·6

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	12	13	14	15	16	17	18	19	20	21	22	23	24
Diabetic Bread	11	15	11	16	11	11·5	12·5	14	12	11	12	13	13
Butter	2	2	2	2	2	2	2	2	2	2	2	2	2
Meat	5	6	5	9	7	5	6	6	5	6	—	—	11
Custard	9	9	9	9	9	9	9	9	9	10	9	9	8
Eggs	2	2	2	2	2	2	2	2	2	2	2	2	2
Bacon	1	1	2	—	3	3	1	2	2	3	1	1	1
Sardines	—	—	—	—	—	—	—	—	—	—	—	—	—
Milk	45	55	25	65	50	75	55	45	45	20	45	55	55
Fish	—	—	—	—	—	—	—	—	—	—	10	—	—
Greens	3	6	3	6	6	6	6	6	6	6	6	6	6
Tea	50	55	50	40	50	50	50	50	50	50	50	50	50
Lemonade	10	30	15	25	30	20	30	20	10	30	10	—	—
Water	10	30	15	25	30	20	30	20	20	30	25	20	20
Lemco	1·3	—	—	—	—	—	0·5	0·5	0·5	0·5	0·5	—	1
Potato	3	4	4	6	5	5	5	5	5	5	5	5	5
Cheese	—	4	—	2	2	2	2	2	2	2	1	1	1
Total urine c.c.	4,010	4,120	3,110	4,710	3,500	4,260	4,040	3,920	3,890	3,390	4,010	3,260	3,930
Total sugar grm.	195·4	211·7	161·5	237·5	220·3	235·8	224·8	213·3	196·5	209·5	192·3	171·2	210·1
Total nitrogen grm.	31·9	29·4	24·5	33·5	27·3	33·8	28·4	30·9	31·0	26·9	30·0	25·7	27·6
Total oxy-butyric grm.	26·4	31·3	24·8	34·4	14·7	28·6	23·0	26·2	25·0	15·2	20·9	18·8	19·1
Total acidity c.c. N. acid	171	136	107	158	116	143	124	153	139	115	141	109	137

Diet.

	12	13	14	15	16	17	18	19	20	21	22	23	24
Carbohydrate grm.	84·5	106·7	69·5	127·5	101·4	126·8	108·3	100·3	97·7	72·7	103·4	108·9	107·9
Nitrogen grm.	33·9	45·8	26·7	50·4	39·4	41·5	41·0	41·4	27·5	34·6	38·2	30·7	48·3
Fat grm.	233·3	316·8	225·9	309·3	283·1	310·0	276·5	293·3	273·9	259·4	241·1	257·3	281·4

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	25	26	27	28	29	1	2	3	4	5	6	7	8
Diabetic Bread	14	11·5	10	12	13	12	9	8	9	10	13	9·5	9
Butter	2	2	2	2	2	2	1	1	1·75	1·5	1	2	1
Meat	10	6	—	6	—	—	6	6	6	6	9	4	—
Custard	8	7	9	9	9	9	9	10	9	9	10	10	10
Eggs	2	2	2	2	2	2	2	2	2	2	2	2	2
Bacon	1	3	2	1	1	2	1	3	2	1	1	1	1
Milk	55	40	55	45	85	55	60	55	55	55	40	60	25
Fish	—	—	12	—	10	16	—	8	—	—	—	—	13
Greens	6	6	6	6	6	6	6	4	7	6	6	.6	3
Tea	50	50	50	50	50	50	50	50	50	65	50	50	65
Lemonade	15	25	10	20	10	10	10	—	—	10	—	10	—
Water	5	25	20	20	20	10	20	10	15	20	35	25	15
Lemco	0·5	0·5	0·5	0·5	0·5	0·5	0·5	0·5	0·5	0·5	0·5	0·5	—
Potato	5	5	5	5	5	5	5	5	5	5	5	5	5
Cheese	2	1	2	1	2	—	1	2	2	5	2	3	—
Total urine c.c.	5,820	4,910	4,600	4,060	4,120	4,340	3,260	3,860	3,590	4,620	3,470	2,530	4,020
Total sugar grm.	341·5	285·3	239·4	212·5	224·6	222·2	187·9	228·7	189·9	247·9	186·2	134·1	216·1
Total nitrogen grm.	37·5	39·7	34·9	31·7	30·0	38·1	26·4	30·8	28·4	37·0	24·9	21·0	32·1
Total oxy-butyric grm.	28·7	27·5	25·9	26·8	15·7	22·1	17·2	15·2	24·0	27·2	21·4	17·5	19·8
Total acidity c.c. N. acid	162	174	162	151	137	139	109	119	134	163	111	95	134

Diet.

	25	26	27	28	29	1	2	3	4	5	6	7	8
Carbohydrate grm.	109·2	90·1	105·0	97·7	138·6	107·6	108·7	101·9	104·5	105·0	95·1	110·3	80·1
Nitrogen grm.	48·7	36·3	28·9	37·7	36·8	29·0	36·5	36·2	37·3	41·5	44·1	35·5	32·9
Fat grm.	297·1	268·0	254·3	253·6	294·1	252·4	241·7	265·7	259·7	283·7	275·5	261·8	189·7

Case IV. W. H. R. Aged 15. Cabinet-maker's apprentice.

Admitted 24/x/13—on account of excessive thirst.

Noticed two months ago that he was very tired after a day's work. One month ago had a bad bilious attack three hours after breakfast; vomited three times that day; was better in the evening, and quite well next day except for feeling very tired.

Since then very weak, especially in the legs: had aching pain in lower part of back.

On 18/x/13 consulted doctor on account of thirst. Glycosuria discovered.

Lately has lost a little weight: constipated during the last few days. Sleep—good. Appetite—good. No cough except a slight one during the last week.

P. H. Bad indigestion frequent: pain in lower chest; onset two to three hours after food. Chicken-pox and measles at age 7.

F. H. Father died aged 59: malignant disease of bladder. No history of diabetes or of exophthalmic goître.

P. C. Not healthy looking. Cheeks high colour. Skin and hair dry.

Tongue large and pale—indented by teeth. Teeth—fair.

Blood pressure 138 mm. Hg. No enlargement of thyroid.

Thorax—symmetrical; heart and lungs normal.

Abdomen—nothing abnormal.

Knee-jerks present and no oedema of legs.

Leowi's reaction $\pm$: later negative.

During his stay in the hospital the patient complained of no symptoms, and on examination nothing abnormal was found beyond the abnormalities of the urine. During the first week he had a little pain in the left iliac fossa associated with emptying of lower bowel of scybalous masses.

This description of the patient I owe to the kindness of Dr. Garrod.

	Weight.			No stool.	
	st.	lb.			
24/x/13	7	11	(49·4 K.)	x/13	26, 28
27 ,,	7	11		xi/13	2, 14, 21, 24
3/xi/13	7	12		xii/13	10, 15, 28.
10 ,,	7	10·5			
17 ,,	8	1·5			
24 ,,	8	2		The patient took 2 oz. (57 grm.)	
1/xii/13	8	3·5		of sodium bicarbonate while	
8 and 15 ,,	8	2·5		he was in the hospital.	
22 ,,	8	4			
30 ,,	8	7			
6/i/14	8	6·5			
11 ,,	8	5 (53·1 K.)			

During his stay in hospital this patient improved considerably and for some time before his discharge he felt very well indeed. I am informed that he was brought to the hospital in a comatose condition about fifteen months after his discharge at the conclusion of these determinations. He had not undergone any further treatment at the hospital.

The table gives particulars of his diet, and of the determinations made on his urine. All these are plotted on the curve.

All the articles of food in this diet, except eggs and fish, were analysed by me on samples sent by the Ward Sister.

The following articles are either not included in S. G.'s diet or are so different as to require special notice—for example, the milk was poorer: it was so poor that the analysis was repeated :

Percentages.

	Carbohydrate.	Nitrogen.	Fat.
Apple	9·4	0·013	—
Ham	—	3·17	33·7
Meat	—	4·64	15·6
Diabetic bread	4·6	4·52	25·4
Bacon	—	0·92	52·7
Cream	1·7	0·249	51·4
Milk	2·5	0·45	2·8
Veal broth	—	0·189	0·1
Onions	8·3	0·17	0·14

The acetoacetic acid was determined throughout this case by the Messinger-Huppert method, and acetone and acetoacetic acid are expressed as acetoacetic acid.

This patient came to the hospital with very high sugar, nitrogen, oxybutyric acid, and acetoacetic acid excretions. It was decided to reduce the carbohydrate very slowly, and the patient was allowed to eat diabetic bread freely—which he did. The reduction of carbohydrate appears to have been entirely beneficial until 10/xi, when it stood at about 100 grm.; and perhaps it would have been better if it had remained at that level for some time before making a further reduction. But the reduction was continued slowly, and now with a rise of the oxybutyric acid and acetoacetic acid so insidious that it was almost unnoticed until 17/xi. The last white bread was taken on 13/xi, but the patient was still allowed 1 litre of milk, and custard made with ordinary milk, and some apple. The rise of acid on 17/xi is unquestionably due to the reduction of the milk by 500 c.c. We have in this case a reproduction of the state of S. G. on 13 to 21/xii/11. Once more the case shows perfectly clearly that on a diet rich in protein and fat a diabetic will develop an uncontrollable acid production uuless he is also given a certain proportion of carbohydrate: on a diet such as this the carbohydrate cannot at once be lowered beyond about 100 grm. without grave risk. It is possible that by keeping the patient for a long time at 100 grm. a further reduction might have been made with very great care : but I incline to the view that carbohydrate cannot be permanently removed from the diet of a diabetic without injury to the patient.

To counteract the acid production, the patient was placed on the von Noorden oatmeal diet. Unfortunately on 23/xi W. H. R. did not eat all his oatmeal, so that the diet cannot be plotted, and the fat in the curve is only approximate: the other four days of the treatment are all correctly shown by the figures. The effect on the excretions is very remarkable; the nitrogen alone remains considerable throughout and the sugar is high on the oatmeal day only. On 24/xi no oxybutyric acid could be found by rotation, but the ether extract gave 4 grm. total acid reckoned on oxybutyric. In the ether extract there are always other acids beside oxybutyric—in it I have found formic and benzoic acids and traces of oxalic acid. On 25/xi the acid was just detectable; but on this day sugar could not be detected in the polarimeter (2 d.c.m. tube), and it could only be estimated with difficulty by Benedict's method—the figure in the curve is the reduction figure. After the treatment the sugar returns at once nearly to its former value with a tendency to rise : the oxybutyric acid rises in stages to its former height. Now the treatment was applied again, except that on 8 and 9/xii, 835 grm. of potato was given on two days instead of a large amount of oatmeal on one day. This time the oxybutyric acid vanished on the second potato day and did not reappear until 12/xii ; the acetoacetic acid was greatly reduced, and the sugar vanished for one day—on 11/xii. After this second treatment the oxybutyric acid rose with great rapidity in spite of the fact that 50 grm. of potato were added to the diet on 13/xii ; but on 17/xii with 100 grm. of potato and 110 grm. of apple the acid begins to fall and continues to do so. Towards

the end of this stage R. received less diabetic bread also.   During the Christmas recess a quantitative diet could not be maintained ;. but on 27/xii it was started again and the analyses were resumed on 29/xii.   An attempt was made now to keep the diet very constant in order to try the effect of administering glycocoll ; in the twelve days 30/xii/13 to 10/i/14 the most serious changes of diet are : on 2/i/14 the meat is raised from 50 to 100 grm ; on 7 and 8/i/14 the diabetic bread is raised from 240 to 300 grm.   Disregarding these changes for the moment we have a fore-period of four days, a glycocoll period of four days, and an after-period of four days.   On each of the glycocoll days no less than 37·5 grm. of the substance were taken.   This corresponds to 7·0 grm. of nitrogen, and, if we assume that all the carbon of glycocoll is converted into sugar, we ought to get 30 grm. of sugar.   The averages for each four-day period are given in the following table :

| | | Fore-Period. | | Glycocoll. | | After-Period. | |
| | | 4 days' average. | | 4 days' average. | | 4 days' average. | |
		in urine.	in food.	in urine.	in food.	in urine.	in food.
Sugar	grm.	78·4	71·9	103·5	70·8	96·7	70·0
Nitrogen	,,	17·0	24·9	25·5	32·6	21·7	27·5
Oxybutyric	,,	8·7		6·1		11·9	
Acetoacetic	,,	4·8		4·0		5·2	
Urine	c.c.	1820		2210		2020	

So the nitrogen of the glycocoll period exceeds that of the fore-period by 8·5 grm., and the sugar of the glycocoll period exceeds that of the fore-period by 25·6 grm.   Subtracting the glycocoll nitrogen from the food nitrogen we have (32·6 − 7) = 25·6 ; that is, 0·7 grm. a day more than in the fore-period, thus reducing the excess in the glycocoll period to (8·5 − 0·7) = 7·8 grm.   The remaining excess of 0·8 grm. N. is no doubt due to the increased volume of urine.   During the glycocoll period the day's urine averages 390 c.c. more than during the fore-period.   Now this introduction of a large quantity of an electrolyte such as glycocoll into the blood-stream would undoubtedly increase the osmotic pressure of the blood ; and the excess of it not utilized by the cells would probably be oxidized to other substances which would also be electrolytes—for example, to ammonia, glyoxylic acid, and formic acid.   This increase of osmotic pressure would cause an increase of the volume of the blood, and the attempt to maintain a constant percentage of blood-sugar would lead to the production of more sugar, not necessarily from the glycocoll.   The ensuing diuresis would then account for the increased urinary sugar.   I believe the increased sugar output of the glycocoll period is to be explained in this way rather than by an approximately quantitative conversion of the glycocoll carbon into glucose.

Embden and Salomon (38) found that glycocoll, when administered to depancreatized dogs, caused an increased excretion of sugar.   Lusk (39) on giving the substance to fully phloridzined dogs found that it caused an increase in the excretion of sugar quantitatively equal to the amount that would be formed if all the carbon of the glycocoll were converted into glucose.

I do not doubt either of these results for a moment, but I do doubt the quantitative conversion of glycocoll into sugar.   When glycocoll is oxidized by a substance such as alloxan (40) or hydrogen peroxide (41) it readily yields ammonia, formaldehyde, formic acid, glyoxylic acid, and other products.

Administered glycocoll could scarcely be expected entirely to escape some such oxidation in the body, and this would lead us to assume the quantitative conversion of each of these oxidation products into sugar—an assumption I am not prepared to make.   Moreover, Sansum and Woodyatt (42) were unable to satisfy themselves that a substance, which is known to be easily condensed to

a mixture of hexoses, namely glycollic aldehyde $\begin{matrix} \text{CHO} \\ | \\ \text{CH}_2\text{OH} \end{matrix}$, when given to a phloridzined animal, produced glucose at all.

The administration of glycocoll to this patient produced a slight fall in the excretion of both oxybutyric and acetoacetic acids; it is difficult to say whether this is a really antiketogenous effect, but I incline to the view that it is, because otherwise, with the increased diuresis and the increased possibility of ammonia formation from glycocoll, an increased excretion of acids might fairly have been expected. The glycocoll effect is well seen on the curve.

In this case it will be noticed that the acetoacetic acid has been determined every day, and the case is quite obviously a typical 'severe' case of diabetes mellitus. It has been stated above that Magnus-Levy regards the acetoacetic acid in such cases as subject to large and inexplicable oscillations from day to day. No such variations occur in this case unless there is some obvious explanation for them such as an abrupt change in the diet, nor, with the same reservation, do they occur in any of the other cases examined by me. The variable is the oxybutyric acid, and this substance is indeed subject to great fluctuations—but even then not to such oscillations as were found by Magnus-Levy in his cases (compare his figures quoted on p. 312).

Neubauer (43) assumes that in the healthy organism oxybutyric acid is constantly being formed and converted into acetoacetic acid, and the latter acid smoothly burnt to carbon dioxide and water; but in the diabetic organism the oxidation of the acetoacetic acid in part is inhibited, so that if the reaction

$$CH_3CHOHCH_2COOH + O = CH_3COCH_2COOH + H_2O$$
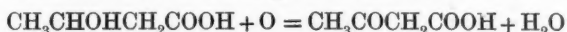
is a reversible one, as Neubauer assumes it to be, there should be an equilibrium point, and a fairly constant ratio of oxybutyric acid to acetoacetic acid might be expected in the tissues and consequently in the urine. On looking through his own cases and those of other recent workers he found that the oxybutyric acid, when expressed as a percentage of the total acetone bodies, all calculated as acetone, excreted in the urine, was remarkably constant and amounted to 60 to 80 per cent. He gives no details of his cases.

Kennaway (44) has published a fine series of cases, for which he has given the details and calculated the ratio

$$\frac{\text{oxybutyric acid expressed as acetone}}{\text{(acetoacetic acid + acetone + oxybutyric acid) all as acetone}} \times 100,$$

which he calls the 'β-ratio'. He extends Neubauer's limits for the ratio, finding 40·2 to 83·6.

I regret that I cannot follow Neubauer and Kennaway in their method of calculation. I prefer, for reasons which will appear below, to express my results simply thus:

$$\frac{\text{acetoacetic acid}}{\text{oxybutyric acid}} \times 100,$$

that is, to express the acetoacetic acid as a percentage of the oxybutyric acid. This way has also the advantage of expressing the number of molecules of acetoacetic acid as a multiple (100) of the molecules of oxybutyric acid without sensible error, for the molecular weights of the two acids only differ by two. The

following formula allows one method of expression to be calculated from the other :

$$\frac{\text{acetoacetic acid}}{\text{oxybutyric acid}} \times 100 = \left(\frac{100}{\beta} - 1\right) \times 98 \cdot 1.$$

Before discussing the results in this case it should be pointed out that the reaction, whose equation is given above, is not a reversible reaction ; acetoacetic acid is not reconverted into oxybutyric acid by combination with water, so that its reversibility cannot form an argument for a constant ratio between aceto-acetic acid and oxybutyric acid. In the case of W. H. R. I have worked out the acetoacetic acid as a percentage of the oxybutyric acid for every day, but instead of recording the percentage for each day I have arranged them on the following plan.

Those for all the days on which the oxybutyric acid is below 5 grm. : those for all the days on which the acid is 5 grm. or more but less than 10 grm. : those for the days when the acid is 10 grm. or more but less than 15 grm., and so on. The figures for each interval are then averaged. In the first period, when the oxybutyric acid is absent and acetoacetic acid is present, the figure for the percentage is infinite, so that for the first period I give each value : on eleven days the oxybutyric acid was below 5 grm., and on four of these it was nothing, so we have ∞ , ∞ , ∞ , ∞ , 157, 130, 129, 125, 100, 100, 82.

			Average Percentage.	
1st Period.	Acid	< 5	Above 100	(11 days)
2nd „	„	5 to < 10	64·5	(19 days)
3rd „	„	10 to < 15	51·0	(14 days)
4th „	„	15 to < 20	39·6	(7 days)
5th „	„	20 to < 25	36·0	(9 days)
6th „	„	25 to < 30	33·4	(9 days)

Thus it appears that the acetoacetic percentage is very high in this case at the onset of acidosis, and it is probably so in all cases. See Table, p. 393. At first it falls rapidly, then slowly, and in this particular case it tends to a limit at about 33 per cent. A discussion of this point will follow later in the paper.

I am indebted to Dr. G. Graham for a series of ammonia determinations in this case, and I wish to express my thanks to him for allowing me to use them. In the following table the ammonia nitrogen is recorded as a percentage of the total nitrogen, its equivalent of oxybutyric acid is calculated, and the sum of the acetoacetic and oxybutyric acids is contained in the third column. Side by side with the figures in this case are placed all those available for the purpose relating to the two most important of Magnus-Levy's cases—both ' cured ' by the bicarbonate of soda treatment. In the case of W. H. R. the ammonia is seen to be sufficient to neutralize both acids on nearly every day ; in Magnus-Levy's cases the ammonia, even on the days he calls normal days, is quite inadequate for the purpose, and only reaches half the required amount on one occasion, and, in fact, on all the coma days in the case of the boy and on one of the two coma days in the case of the girl it is not sufficient for the neutraliza-tion of the acetoacetic acid alone—on two of these days not half enough. It

cannot be said that the soda is responsible for the great differences in the cases, for W. H. R. took large quantities of soda, larger than the girl on other than coma days, and larger than the boy on 'normal days'. I am of opinion that these results show that a rich protein diet is a real asset to a diabetic, and also that W. H. R. took considerably more soda than was necessary or even good for him. The continuous administration of large amounts of soda must, by its mere mass action, remove other indispensable metals from the body. For example, M.-L.'s boy lost large amounts of potassium. See p. 392.

W. H. R. Boy 15.				Magnus-Levy's case. Boy 13.				Magnus-Levy's case. Girl 12.			
Date.	I.	II.	III.	Date.	I.	II.	III.	Date.	I.	II.	III.
17/xii	18·6	35·5	34·0	†5/vii	10·8	15·4	74·9	21/ii	26·7	25·4	40·3
18 ,,	19·0	37·5	36·8	†6 ,,	11·1	15·6	115·4	†23 ,,	18·0	22·1	93·3
19 ,,	19·0	29·4	28·4	†7 ,,	15·3	17·2	142·8	†24 ,,	7·2	11·5	107·6
21 ,,	18·8	31·6	32·6	†8 ,,	25·2	17·6	83·0	26 ,,	13·7	21·2	45·8
23 ,,	18·8	24·5	20·7	13–14	15·1	12·5	34·3	27 ,,	11·6	17·2	53·9
31 ,,	11·1	14·7	12·1	21–24	17·7	19·3	42·6	28 ,,	14·3	19·5	56·8
1/i	10·9	7·7	12·3	†2/viii	10·5	12·9	88·6				
*4 ,,	7·6	16·0	11·7	†3 ,,	11·5	13·7	73·1				
*5 ,,	6·8	13·2	11·4	5–8 ,,	20·7	26·4	59·6				
*6 ,,	6·6	12·9	8·9								
8 ,,	8·5	10·4	8·8								
9 ,,	10·4	21·5	26·3								

* Glycocoll days.   † Coma days.

Column I gives $\dfrac{\text{ammonia nitrogen}}{\text{total nitrogen}} \times 100$.

,,   II   ,,   ammonia nitrogen calculated as oxybutyric acid.
,,   III   ,,   sum of acetoacetic and oxybutyric acids.
W. H. R. took 56 grm. of bicarbonate every day.
M.-L.'s boy took bicarbonate 60, 210, 90, 80, 40, 40, 200, 90, 40.
,,   girl   ,,   ,,   18, 109, 102 ?, 36, 36, 36.

The D : N ratios have been calculated for the periods 5 to 16/xi : 27/xi to 5/xii : 15/xii to 23/xii.

They are 2·96, 2·59, 2·53, or corrected as in the preceding cases 3·1, 2·76, 2·7. They do not show a maximum production of sugar from protein, so that the protein in this patient's diet was no doubt higher than was necessary; but it is to be remembered that he ate these amounts of protein of his own free will— there was no attempt made to urge the boy to take so high a protein diet. Attention is again drawn to the fact that in spite of the exceeding richness of the diet in fat there is no tendency for the oxybutyric acid to rise until the carbo-hydrate is reduced below a certain amount. Again, on 8/xii, there is a sudden rise in the food fat from 117 to 200 grm. for two days, but in spite of this the two acids decrease. Then from 29/xii/13, with about 250 grm. of fat in the diet, the acetone bodies are low, with only 70 grm. of carbohydrate in the diet.

The curve is plotted exactly like the preceding ones.
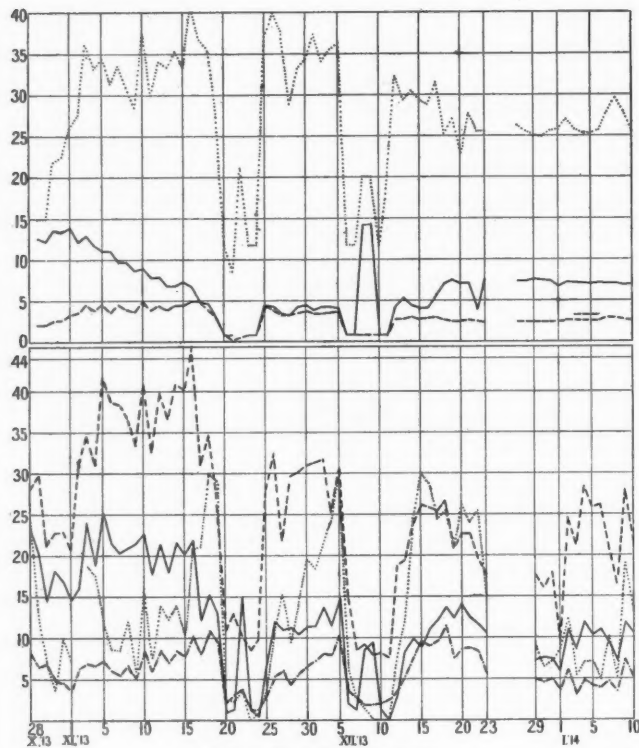
Curve IV. Case W. H. R.

		OCTOBER, 1913.			NOVEMBER, 1913.					
	28	29	30	31	1	2	3	4	5	6
Greens	—	120	100	100	120	120	120	160	175	120
Apple	—	120	160	150	135	115	95	90	105	160
W. bread	—	140	130	150	140	140	110	110	90	70
Milk	—	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000
Custard	—	170	150	170	220	200	220	130	280	220
Egg	—	1	2	2	2	2	2	2	2	2
D. bread	—	40	50	90	160	300	325	515	370	460
Meat	—	150	120	120	100	100	150	125	120	105
Fish	—	—	—	—	—	—	—	—	—	—
Cheese	—	—	—	40	20	35	—	30	25	20
Ham	—	—	—	—	40	40	—	70	—	85
Sardines	—	10	20	50	—	—	100	35	90	—
Bacon	—	50	50	50	60	35	70	85	110	65
Butter	—	50	45	55	75	85	70	90	95	105
Total urine c.c.	3,695	3,000	2,560	3,210	3,120	2,630	2,940	3,900	3,320	3,870
Total sugar grm.	229·1	202·8	153·5	170·5	153·0	143·0	151·1	244·3	192·2	237·6
Total nitrogen grm.	28·1	29·6	21·1	22·7	22·9	30·8	30·9	34·5	31·0	41·7
Total oxybutyric grm.	24·2	12·4	7·0	3·7	9·8	7·4	—	18·7	17·6	11·9
Total acetoacetic grm.	8·1	6·5	6·8	4·8	4·6	3·5	6·2	6·9	6·7	7·2
Diet.										
Carbohydrate grm.	—	125·8	123·3	136·1	134·4	138·3	121·5	127·8	117·0	111·3
Nitrogen grm.	—	19·7	19·7	24·5	26·2	32·8	36·5	44·9	38·7	45·0
Fat grm.	—	148·5	149·5	218·2	224·7	259·5	275·3	360·8	333·3	344·3

NOVEMBER, 1913.

	7	8	9	10	11	12	13	14	15	16
Greens	150	245	155	165	120	120	120	120	120	150
Apple	145	115	195	125	170	140	220	145	120	140
W. bread	70	40	40	30	20	20	10	—	—	—
Milk	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000
Custard	235	175	210	220	250	250	150	200	200	225
Egg	2	2	2	2	2	2	2	2	2	2
D. bread	430	555	435	460	550	380	410	410	465	500
Meat	—	105	100	75	170	130	175	105	150	140
Fish	135	—	—	—	—	—	—	—	—	—
Cheese	20	20	15	—	35	35	30	35	35	35
Ham	60	85	55	—	70	50	110	80	85	—
Sardines	85	—	50	75	35	50	65	50	60	100
Bacon	75	55	50	55	85	75	85	100	100	70
Butter	80	75	85	70	80	60	65	70	65	75
Total urine c.c.	3,560	3,310	3,180	2,980	4,020	2,880	3,630	3,140	3,620	3,500
Total sugar grm.	211·8	206·4	199·5	206·5	227·3	169·4	191·4	168·6	206·1	190·6
Total nitrogen grm.	38·7	38·3	36·7	33·3	40·7	32·6	39·9	36·7	40·9	40·1
Total oxybutyric grm.	8·6	8·5	11·9	5·9	16·0	7·6	13·8	12·2	13·8	10·4
Total acetoacetic grm.	6·1	5·6	6·6	5·3	8·4	6·1	8·3	7·0	8·5	7·8

Diet.

	7	8	9	10	11	12	13	14	15	16
Carbohydrate grm.	110·1	96·7	97·5	87·1	89·5	78·8	78·6	67·7	67·9	73·3
Nitrogen grm.	36·2	44·1	38·7	37·0	48·0	38·4	42·9	39·2	44·0	43·7
Fat grm.	313·8	334·9	309·6	283·9	374·6	299·3	339·7	333·9	352·4	333·1

NOVEMBER, 1913.

	17	18	19	20	21	22	23	24	25	26
Greens	150	150	135	120	300	300	—	300	300	150
Apple	125	140	180	85	—	—	—	—	—	100
Milk	500	150	—	—	—	—	—	—	—	—
Custard	370	220	220	220	—	—	—	—	—	220
Egg	2	2	2	2	5	—	5	5	5	2
D. bread	550	440	420	295	—	—	—	—	—	490
Meat	185	185	170	125	—	—	—	—	—	170
Cheese	—	50	35	35	—	—	—	—	—	50
Ham	85	70	75	35	—	—	—	—	—	50
Sardines	130	100	100	80	—	—	—	—	—	100
Bacon	85	100	100	100	—	—	—	—	—	150
Butter	110	100	95	72	100	100	200	100	100	75
Cream	—	100	135	—	—	—	—	—	—	—
Veal broth	—	—	—	—	600	600	—	600	600	—
Lemonade	—	—	—	—	300	550	100	300	600	+
Coffee	—	—	—	—	900	1,000	1,300	1,400	1,000	+
Tea	—	—	—	—	350	400	800	400	400	+
Water	—	—	—	—	300	—	1,300	—	—	+
Oatmeal	—	—	—	—	—	—	{ 250 & 1,200 c.c. H_2O	—	—	—
Oatmeal biscuits	—	—	—	—	—	—	1 doz.	—	—	—
Total urine c.c.	3,920	2,600	3,250	2,780	1,125	1,820	3,340	2,200	2,060	2,800
Total sugar grm.	198·9	111·9	134·3	116·2	2·7	6·1	139·3	8·4	0·0	56·0
Total nitrogen grm.	45·3	30·9	34·6	26·8	10·8	12·9	10·4	8·6	9·8	27·6
Total oxybutyric grm.	20·8	21·1	29·9	29·0	5·4	2·4	3·6	0·0	0·7	5·6
Total acetoacetic grm.	10·2	8·0	10·8	9·4	2·2	3·0	3·6	1·2	1·1	3·2

Diet.

	17	18	19	20	21	22	23	24	25	26
Carbohydrate grm.	66·6	48·4	47·5	31·3	8·1	8·1	?	8·1	8·1	43·6
Nitrogen grm.	49·5	48·4	39·5	29·8	7·9	2·5	—	7·9	7·9	43·0
Fat grm.	406·9	366·6	352·6	272·6	117·1	84·7	—	117·1	117·1	371·4

	NOVEMBER, 1913.				DECEMBER, 1913.				
	27	28	29	30	1	2	3	4	5
Greens	150	150	150	150	150	150	150	150	150
Apple	75	55	65	145	140	110	145	140	125
Potato	—	—	—	—	—	—	—	—	—
Custard	220	200	220	220	220	220	220	220	220
Egg	2	2	2	2	2	2	2	2	2
D. bread	445	320	305	320	365	310	320	335	350
Meat	115	125	170	190	170	130	170	135	130
Cheese	60	50	40	—	50	50	25	50	55
Ham	75	60	60	70	70	70	50	80	80
Sardines	70	70	70	70	70	100	100	85	100
Bacon	60	75	—	115	90	165	100	100	100
Butter	60	60	60	50	45	50	60	60	60
Cream	220	240	130	130	130	130	130	130	130
Veal broth	—	—	—	--	—	—	—	—	—
Lemonade	+	+	+	+	2,100	1,500	800	900	900
Coffee	+	+	+	+	1,000	1,000	1,000	700	1,000
Tea	+	+	+	+	400	400	400	400	500
Water	+	+	+	+	400	800	500	1,300	400
Oatmeal	—	—	—	—	—	—	—	—	—
Oatmeal biscuits	—	—	—	—	--	—	—	—	--
Total urine c.c.	3,450	2,770	2,440	2,580	2,620	2,790	3,140	2,680	3,430
Total sugar grm.	120·5	97·8	102·4	96·5	113·2	113·8	136·1	114·4	148·1
Total nitrogen grm.	32·4	21·8	29·6	30·1	31·0	31·3	31·6	25·2	30·7
Total oxybutyric grm.	10·6	15·2	9·5	13·9	19·5	18·3	21·3	24·2	29·6
Total acetoacetic grm.	5·3	6·0	4·4	5·6	6·7	7·2	8·1	8·0	10·2
Diet.									
Carbohydrate grm.	42·5	34·5	32·5	42·0	43·6	38·2	42·0	42·2	41·5
Nitrogen grm.	38·4	32·3	32·8	33·8	36·8	34·1	34·1	34·7	35·8
Fat grm.	398·6	376·9	289·0	231·2	344·1	373·7	341·5	355·3	363·0

	DECEMBER, 1913.								
	6	7	8	9	10	11	12	13	14
Greens	300	300	—	—	300	300	150	150	150
Apple	—	—	—	—	—	—	115	150	50
Potato	—	—	835	835	—	—	—	50	50
Custard	—	—	—	—	—	—	170	220	220
Egg	5	5	5	5	5	5	4	4	4
D. bread	—	—	—	—	—	—	380	355	370
Meat	—	—	—	—	—	—	—	50	50
Cheese	—	—	—	—	—	—	—	—	—
Ham	—	—	—	—	—	—	—	—	—
Sardines	—	—	—	—	—	—	95	50	100
Bacon	—	—	—	—	—	—	—	—	50
Butter	100	100	200	200	100	200	115	105	70
Cream	—	—	—	—	—	—	160	130	130
Veal broth	600	600	—	—	600	600	—	—	—
Lemonade	500	300	300	—	—	200	300	1,000	200
Coffee	1,150	1,100	1,500	1,500	1,100	1,100	700	700	500
Tea	400	400	800	800	400	400	800	400	1,200
Water	—	—	200	—	200	—	—	400	300
Total urine c.c.	2,040	1,290	2,480	2,420	2,030	1,610	1,725	3,050	2,590
Total sugar grm.	18·6	11·5	86·2	93·0	11·7	0·0	27·1	83·2	98·5
Total nitrogen grm.	15·0	8·7	9·2	7·9	8·2	7·7	18·8	19·3	23·8
Total oxybutyric grm.	6·3	2·6	1·4	0·0	0·0	Trace	13·9	23·8	29·9
Total acetoacetic grm.	3·4	2·6	1·8	1·2	2·0	2·7	3·6	5·4	7·6
Diet.									
Carbohydrate grm.	8·1	8·1	142·3	142·3	8·1	8·1	40·6	52·6	43·9
Nitrogen grm.	7·9	7·9	7·6	7·6	7·9	7·9	27·0	27·4	30·0
Fat grm.	117·1	117·1	200·4	200·4	117·1	201·1	321·6	294·3	305·2

DECEMBER, 1913.

	15	16	17	18	19	20	21	22
Greens	150	150	150	150	150	150	150	150
Apple	50	50	110	100	160	110	110	130
Potato	50	50	100	200	200	200	200	—
Custard	220	220	220	220	220	220	220	220
Egg	4	4	4	3	3	3	3	3
D. bread	300	310	350	290	275	275	275	280
Meat	50	50	50	50	50	50	50	50
Cheese	—	—	—	—	—	—	—	—
Ham	50	50	50	—	50	50	50	—
Sardines	50	70	50	100	60	50	70	100
Bacon	50	50	50	50	50	—	50	50
Butter	70	55	80	40	55	40	60	45
Cream	130	130	130	130	130	130	130	130
Veal broth	—	—	—	—	—	—	—	—
Lemonade	1,000	975	955	1,000	1,600	200	1,000	—
Coffee	700	600	700	700	700	500	500	—
Tea	875	450	400	700	400	400	400	—
Water	—	800	1,000	400	—	1,600	350	—
Total urine c.c.	2,560	2,650	2,780	2,950	2,250	2,590	2,450	2,360
Total sugar grm.	89·0	109·8	122·3	136·3	123·5	139·0	124·2	114·8
Total nitrogen grm.	26·2	26·0	25·6	26·5	20·7	22·6	22·6	19·6
Total oxybutyric grm.	29·9	28·8	24·4	25·4	20·9	26·2	24·0	25·4
Total acetoacetic grm.	9·7	9·1	9·6	11·3	7·5	8·6	8·6	8·4
Total ammonia grm.	—	—	5·8	6·1	4·8	—	5·2	—
Diet.								
Carbohydrate grm.	40·7	41·1	57·1	70·5	75·4	70·7	70·7	38·8
Nitrogen grm.	26·9	28·0	29·3	25·7	25·5	24·7	25·8	24·8
Fat grm.	294·2	288·2	315·3	253·2	270·8	229·8	277·0	254·9

DECEMBER, 1913. | JANUARY, 1914.

	23	24th, 25th, and 26th not weighed.	27	28	29	30	31	1	2
Greens	150		120	150	150	150	150	150	150
Apple	165		170	155	165	170	160	75	140
Potato	200		200	200	200	200	200	200	200
Custard	220		220	220	220	220	220	220	220
Egg	3		3	3	3	3	3	3	3
D. bread	255		250	255	255	240	240	260	250
Meat	50		50	50	50	50	50	50	100
Cheese	—		—	—	—	—	—	—	—
Ham	50		50	50	50	50	50	50	50
Sardines	50		60	50	50	60	50	50	50
Bacon	50		50	50	50	50	50	50	50
Butter	45		60	45	40	40	50	45	55
Cream	130		115	130	130	130	130	130	130
Lemonade	1,000		900	1,500	1,000	1,300	1,800	1,400	1,300
Coffee	500		500	500	500	500	500	500	500
Tea	400		450	400	400	400	400	400	500
Water	200		1,100	400	400	300	—	200	400
Glycocoll	—		—	—	—	—	—	—	—
Total urine c.c.	1,930	—	—	—	2,350	1,640	2,060	1,150 ?	2,420
Total sugar grm.	105·2	—	—	—	73·3	74·8	73·7	57·5	107·7
Total nitrogen grm.	17·6	—	—	—	17·6	16·1	17·8	9·4	24·7
Total oxybutyric grm.	14·9	—	—	—	8·8	6·7	7·2	8·6	12·2
Total acetoacetic grm.	5·8	—	—	—	4·9	4·6	4·9	3·6	6·1
Total ammonia grm.	4·0	—	—	—	—	—	2·4	1·3	—
Diet.									
Carbohydrate grm.	75·0	—	73·9	74·0	76·0	74·7	73·8	66·8	72·4
Nitrogen grm.	24·2	—	24·2	24·2	23·9	23·6	24·5	26·2	25·4
Fat grm.	255·3	—	261·6	255·3	251·1	249·3	255·7	256·5	270·2

JANUARY, 1914.

	3	4	5	6	7	8	9	10
Greens	150	150	150	150	150	150	150	150
Apple	135	130	120	140	100	100	100	120
Potato	200	200	200	200	200	200	200	200
Custard	220	220	220	220	220	220	220	220
Egg	3	3	3	3	3	3	3	3
D. bread	230	230	230	240	300	300	250	230
Meat	100	100	100	100	100	100	120	100
Cheese	—	—	—	—	—	—	—	—
Ham	50	50	50	50	50	50	50	50
Sardines	50	50	50	60	50	50	50	60
Bacon	50	50	50	50	50	50	50	50
Butter	45	40	40	40	50	70	60	40
Cream	130	130	130	130	130	130	130	130
Lemonade	1,250	850	1,400	800	600	900	600	800
Coffee	500	500	500	500	500	500	500	500
Tea	400	400	400	450	400	500	500	400
Water	—	250	—	400	800	300	400	600
Glycocoll	37·5	37·5	37·5	37·5	—	—	—	—
Total urine c.c	1,970	2,260	2,430	2,170	1,910	1,500	2,700	1,970
Total sugar grm.	84·6	117·9	103·1	108·5	91·7	72·0	118·8	104·2
Total nitrogen grm.	21·2	28·4	25·9	26·3	20·7	16·5	28·1	21·4
Total oxybutyric grm.	5·4	6·9	7·1	4·9	10·0	5·3	19·0	13·1
Total acetoacetic grm.	3·0	4·8	4·3	4·0	4·7	3·5	7·3	5·3
Total ammonia grm.	—	2·6	2·1	2·1	—	1·7	3·5	—
Diet.								
Carbohydrate grm.	71·0	70·5	69·6	71·9	70·9	70·9	68·6	69·6
Nitrogen grm.	32·4	32·4	32·4	33·2	28·6	28·6	27·2	25·7
Fat grm.	256·7	252·5	252·5	257·1	278·7	295·5	277·5	254·6

Case V.   P. B.   Man, 27.   Clerk.

Admitted to the hospital 9/iv/14.

He is a twin; the other twin is alive and well. Two brothers and two sisters died in infancy. One sister died, aged 20, of ' some woman's complaint'. There are five brothers, not counting the twin, all alive and well.

Father alive, aged 61 ; he had glycosuria three months before P. B. had it, but the condition disappeared after three months' treatment and has not reappeared ; he eats anything except what actually contains sugar.

Mother, aged 60, is alive and well.

No other diabetic in the family : no history of consumption or cancer.

Symptoms of thirst and weakness led his doctor to suspect diabetes in May, 1912. Has had restricted diet ever since. Has periods of thirst and pain in his legs: at other times he is pretty well. At Christmas, 1913, he underwent a kind of starvation treatment which did him no good! he lost a stone in weight which he has not regained, and he has passed more water since that treatment. His organs are apparently normal.

His weight was as follows :

| Date.	Weight.
12/iv/14	8 st. 12·5 lb. = 56·47 kilos.
20 ,, ,,	8 ,, 11 ,,
27 ,, ,,	8 ,, 10·5 ,,
4/v/14	8 ,, 9·5 ,,
11 ,, ,,	8 ,, 3·5 ,,
18 ,, ,,	8 ,, 3 ,,
25 ,, ,,	8 ,, 2·5 ,,
1/vi/14	8 ,, 0·5 ,, = 51·03 kilos.

He passed no stool on iv/10, 11, 28 and v/1, 3, 8.

Starting 12/iv he took about 20 grm. bicarbonate of soda every day till 4/v. It was proposed to replace the soda by a smaller amount of potassium bicarbonate; unfortunately through a misunderstanding only about 2 grm. of this salt were taken from 5/v to 27/v. This patient received glucose per rectum—without effect. He also took glycocoll—this will be referred to presently. The weighed diet and determinations were started on 22/iv/14. Particulars of all these are contained in the accompanying table and curve. A glance at the latter shows that the patient is of the severest type, the oxybutyric acid being far above the nitrogen and one-tenth of the sugar; his condition at the beginning of these observations is that of J. H. B. at the outbreak of acid formation, or that of E. E. near the end of that case. The exceedingly high excretion of acetoacetic and oxybutyric acids has unquestionably been occasioned by too great a reduction of the carbohydrate in the diet, whether brought about rapidly or not. When these observations started P. B. was on a fairly rich protein and fat diet, but his carbohydrate was inadequate. A comparison of the diet and excretions in this case with those shortly after the beginning of the preceding case, W. H. R., is of great interest. The latter is on a far richer diet in every respect from 2/xi/13 than is P. B. from 22 to 30/iv/14, but his acid production is insignificant until he reaches P. B.'s level of 80 or less grm. of carbohydrate; then his acid production begins to increase and he would unquestionably have passed into the same category as P. B. had the same treatment continued. At 80 grm. of carbohydrate, then, P. B. is starved in respect of this item of his diet: he produces from his 220 grm. of fat and 28 grm. of protein nitrogen more acetoacetic and oxybutyric acid than he would have done had his carbohydrate been 100 or 120 grm.

On 1/v P. B. was placed on a diet of vegetables, eggs, butter, and milk, with the result that on this diet of only 1,340 calories there is a great reduction in the amount of all the substances excreted. Still keeping the vegetables very high, diabetic bread, bacon, cream, and meat are added to the diet and three eggs are taken away, so that the man is now on a rich fat, low protein, and low carbohydrate diet. As a result the oxybutyric acid nearly resumes its former value, the patient excretes more nitrogen than the diet contains, the excretion of sugar increases practically all the time, and there is a serious fall in body weight. A very similar experiment was made between 11/v and 16/v, except that on 13 and 14/v 140 grm. of carbohydrate in the form of potato were given. The effect of the carbohydrate is very striking: it causes an increase of a litre in the urine on 13/v, but in spite of this the oxybutyric acid only increases by 4 grm., and on 14/v there is a further increase of 600 c.c. in the urine while the acid falls to its lowest value for the whole period of the case. Not only so, but on these two days the sugar excreted is actually less than the carbohydrate consumed, and since a part of the sugar excreted must be assumed to be due to sugar produced from protein it seems to be established beyond a doubt that this diabetic has still the power to deal with a part of his carbohydrate intake. This is another illustration of what has been insisted on before: that no matter how severe the case may be some proportion of carbohydrate is essential for the diabetic. After 16/v P. B. was kept on a constant diet of 46 grm. carbohydrate, 15·8 of nitrogen and 237·6 of fat. At first nitrogen is retained, but afterwards it is lost. The output of sugar increases very seriously, and so do the acetoacetic and oxybutyric acids. Also the patient's weight is inclined to fall. It appears to the writer that the results in this case show quite definitely that if a diabetic is to hold his own he must receive a certain amount of carbohydrate, for a man of 8 st. weight probably at least 100 to 120 grm., and an amount of protein equal to 20 or 25 grm. of nitrogen, and some 200 grm. of fat. Other requirements in the form of bases will be referred to later.

On 24, 25, 26/v P. B. received 37·5 grm. of glycocoll each day. The results of this experiment are as follows :

Average for	Urine.	Sugar.	Nitrogen.	Oxybutyric.	Acetoacetic.
4 days before	3,060	96·4	14·5	31·8	8·1
4 days during	3,240	117·1	20·7	35·0	10·3

In this case there is an increase in the urine excreted of 180 c.c. and an increase of each of the four substances determined; but the increase in sugar is only 21 grm. while before it was 25 grm. with an increase of 390 c.c. in the urine. With the less diuresis there is a lowered output of sugar. The nitrogen which should have increased by 7 grm. increases by only 6·2 grm. The increase in the quantity of the two acids excreted is possibly due in part to a retention of these two substances on the day preceding the administration of the glycocoll. As regards production of sugar from glycocoll this case confirms me in the view I expressed under Case IV, and as regards its antiketogenous action it must at all events be slight. The excretion of acetoacetic acid in this case is worthy of attention—those enormous oscillations in the amount of this substance on which
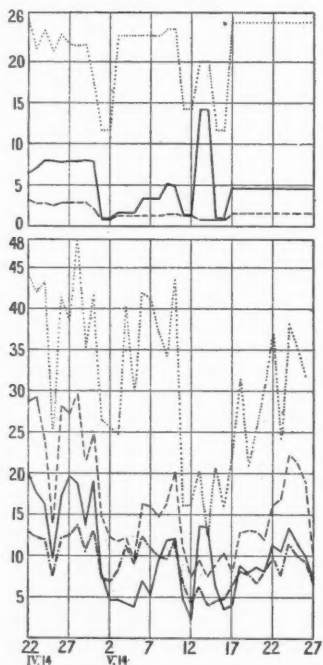
Curve V.   Case P. B.

Magnus-Levy lays such stress are entirely absent. Such variations as occur are accompanied by corresponding variations in all the other urinary constituents determined ; for instance, on 25/iv when there was an obvious retention of urine, on 1/v when this patient passed abruptly to a vegetable diet, and so on. Again Magnus-Levy states (6) that amounts of acetone corresponding to 10 grm. of acetoacetic acid are scarcely ever observed either in or out of coma ; now from 22/iv to 30/iv P. B. excreted less than 12 grm. of acetoacetic acid on two days only, in fact his average for the nine days is 11·8 grm.

The value of the ratio $\dfrac{\text{Acetoacetic acid}}{\text{Oxybutyric acid}} \times 100$ has been calculated for this case (see p. 393). It varies from 33 to 28 and in such a way that for given amounts of oxybutyric acid it is always lower than in the case of W. H. R. In other words P. B. had a greater power of converting acetoacetic acid into oxybutyric acid than W. H. R. had. Some patients have a smaller power of conversion than W. H. R.; so that if, as the writer hopes to show, acetoacetic acid is an important factor in the causation of diabetic coma, we have in this circumstance an explanation of the fact that some patients pass into coma when they are excreting only 20 or 30 grm. of oxybutyric acid while others do so only when they are excreting 50 grm. or more.

I am indebted to Dr. G. Graham, who kept this case under his observation for a long time after it was discharged from the Hospital, for a sample of urine collected on 24/vi, 1914; it measured 6,800 c.c. and contained 71·2 grm. of oxybutyric acid. The explanation of this great increase in the acid is, I believe, due to the circumstance that P. B. was put on a stricter diet by his own doctor.

This patient died in February, 1915.

Diet of P. B.

	APRIL, 1914.									MAY, 1914.		
	22	23	24	25	26	27	28	29	30	1	2	3
Meat	150	120	100	100	100	170	170	130	100	—	—	50
Potato	100	100	100	100	100	100	100	100	100	—	—	—
Ham	50	—	30	—	30	—	—	—	—	—	—	—
Sardines	70	70	—	—	40	—	—	—	—	—	—	—
Greens	230	200	130	200	100	130	130	150	150	360	360	360
Custard	150	200	200	200	200	200	200	200	200	—	—	—
Butter	90	60	80	80	80	80	70	70	55	100	100	100
Diabetic bread	250	220	260	230	230	240	240	230	170	—	—	100
Casoid bread	—	—	—	—	—	—	—	—	—	—	—	—
Cheese	20	—	5	—	20	—	20	20	—	—	—	—
Eggs	2	2	2	2	2	2	2	2	2	5	5	2
Milk	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000
Bacon	—	50	50	40	30	30	30	40	30	—	—	60
Onions	—	80	100	100	100	100	100	100	100	—	—	—
Apple	—	—	70	70	80	70	70	50	70	—	—	—
Glucose per rect.	—	—	—	—	+	—	28·4	42·6	—	—	—	—
Cream	—	—	—	—	—	—	—	—	—	—	—	150
Coffee	500	750	—	650	600	750	700	700	700	1,300	1,675	1,000
Tea	750	750	1,450	800	500	700	750	600	450	350	500	1,250
Lemonade	1,300	1,450	450	1,300	1,600	300	1,050	800	500	500	1,000	1,800
Veal broth	—	—	—	—	—	—	—	—	—	600	600	600
Water	600	750	1,350	450	210	400	1,500	700	350	800	1,800	1,000
Brandy	—	—	—	—	—	—	—	—	—	—	—	—
Total urine c.c.	4,420	3,825	3,635	2,285	3,965	4,030	4,350	3,420	4,145	2,100	2,060	3,050
Total sugar grm.	197·9	176·8	163·8	97·0	172·3	196·1	186·8	137·2	189·1	79·8	47·0	46·9
Total nitrogen grm.	28·7	29·2	24·0	14·0	28·1	27·2	29·6	21·4	24·7	14·6	12·3	11·8
Total oxybutyric grm.	44·0	42·0	43·3	25·4	41·4	38·6	48·3	35·2	41·6	26·5	25·4	24·7
Total acetoacetic grm.	12·9	12·3	12·0	7·6	12·1	12·4	13·7	10·5	12·9	7·4	6·9	8·2
Diet.												
Carbohydrate grm.	65	71	80	80	78	79	79	80	79	10	10	17
Nitrogen grm.	32·1	27·9	27·7	25·5	27·9	28·6	28·9	28·8	22·4	8·2	8·2	12·6
Fat grm.	249	217	238	214	233	222	220	221	172	117	117	232

MAY, 1914.

	4	5	6	7	8	9	10	11	12	13	14	15
Meat	50	50	50	50	50	100	100	—	—	—	—	—
Potato	—	—	100	100	100	200	200	—	—	835	835	—
Greens	360	360	360	360	360	360	300	330	330	—	—	360
Butter	100	100	100	100	100	100	100	100	100	200	200	100
Diabetic bread	100	100	100	100	100	200	200	—	—	—	—	—
Eggs	2	2	2	2	2	2	2	5	5	5	5	5
Bacon	60	60	60	60	60	60	60	—	—	—	—	—
Coffee	950	950	950	950	950	1,000	950	1,000	1,900	2,000	3,000	2,000
Tea	1,300	1,000	1,250	800	1,400	1,550	1,700	1,000	800	2,800	3,000	500
Lemonade	1,000	500	1,000	1,000	800	500	1,000	500	500	200	500	1,250
Veal broth	600	600	600	600	600	600	600	600	600	—	—	600
Water	1,250	—	1,000	700	1,000	1,000	1,000	1,000	1,000	500	500	500
Brandy	—	+	+	—	—	—	—	—	—	—	—	—
Cream	150	150	150	150	150	150	150	—	—	—	—	—
Total urine c.c.	3,520	3,220	4,125	3,030	2,925	3,020	3,930	2,110	2,680	3,725	4,340	2,750
Total sugar grm.	43·2	39·1	68·8	53·3	93·7	118·5	120·6	48·1	24·5	135·9	135·4	63·5
Total nitrogen grm.	12·2	9·7	16·3	15·9	14·8	16·3	20·2	11·3	7·4	9·5	7·5	8·9
Total oxybutyric grm.	40·1	30·0	41·9	41·2	37·2	34·3	43·5	16·2	16·2	20·2	12·6	20·5
Total acetoacetic grm.	11·2	9·0	12·4	10·9	10·0	9·6	11·8	6·6	4·2	6·2	4·1	4·6
Diet.												
Carbohydrate grm.	16·6	16·6	33·6	33·6	33·6	50·7	49·1	13·5	13·5	142·3	142·3	9·7
Nitrogen grm.	12·6	12·6	12·9	12·9	12·9	15·4	15·1	12·5	12·5	7·6	7·6	8·2
Fat grm.	232·4	232·4	232·4	232·4	232·4	240·2	240·2	142·5	142·5	200·4	200·4	117·1

MAY, 1914.

	16	17	18	19	20	21	22	23	24	25	26	27
Meat	·—	50	50	50	50	50	50	50	50	50	50	50
Potato	—	200	200	200	200	200	200	200	200	200	200	200
Greens	360	360	360	360	360	360	360	360	360	360	360	360
Butter	100	100	100	100	100	100	100	100	100	100	100	100
Casoid bread	—	100	100	100	100	100	100	100	100	100	100	100
Eggs	5	4	4	4	4	4	4	4	4	4	4	4
Milk	—	—	—	—	—	—	—	—	—	—	—	500
Bacon	—	60	60	60	60	60	60	60	60	60	60	60
Apple	—	—	—	—	—	—	—	—	—	—	—	100
Cream	—	150	150	150	150	150	150	150	150	150	150	150
Veal broth	600	600	600	600	600	600	600	600	600	600	600	600
Coffee	1,650	1,000	1,700	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000
Tea	1,000	1,700	1,000	1,750	1,000	2,050	1,750	1,750	1,750	1,750	1,750	1,450
Lemonade	1,400	500	700	1,700	1,000	800	500	1,250	500	1,000	1,000	1,000
Water	—	500	1,000	500	500	—	600	600	600	600	600	200
Glycocoll	—	—	—	—	—	—	—	—	37·5	37·5	37·5	—
Total urine c.c.	3,725	2,900	3,050	2,870	3,000	2,890	3,300	3,040	3,860	3,140	2,720	2,050
Total sugar grm.	36·2	41·3	88·4	80·3	85·6	81·8	112·6	105·7	134·2	116·9	100·3	72·7
Total nitrogen grm.	10·4	8·2	12·9	13·1	13·0	11·9	16·1	16·8	22·2	21·3	18·8	9·6
Total oxybutyric grm.	16·1	22·0	31·4	20·9	25·5	30·6	36·7	24·2	38·2	35·0	31·8	—
Total acetoacetic grm.	4·9	6·3	8·1	7·8	6·7	8·2	9·8	7·7	11·4	10·1	9·4	6·6
Diet.												
Carbohyrate grm.	9·7	46·1	46·1	46·1	46·1	46·1	46·1	46·1	46·1	46·1	46·1	46·1
Nitrogen grm.	8·2	15·8	15·8	15·8	15·8	15·8	15·8	15·8	22·8	22·8	22·8	15·8
Fat grm.	117·1	247·6	247·6	247·6	247·6	247·6	247·6	247·6	247·6	247·6	247·6	247·6

Case VI. W. M. G.

This was a private patient of Dr. Garrod's. He was a middle-aged man who had been treated abroad for diabetes. When he came to Dr. Garrod he was on a diet free from carbohydrate. After the first determination of the oxybutyric acid the diet was slightly relaxed. I give the figures, although the patient was not on a weighed diet, because they show what enormous quantities of oxybutyric acid can be excreted over a prolonged period without the patient passing into coma. It should be noticed that the determinations were made about once a week.

Date.	Sugar (grm.).				
1911.	By rotation.	By reduction.	Nitrogen (grm.).	Oxybutyric (grm.).	Volume c.c.
17–18/ii	117·5	162·8	17·7	68·2	4,400
24–25 ,,	142·8	190·2	17·9	56·4	4,125
3–4/iii	136·5	173·7	15·7	54·8	3,720
10–11/iii	131·0	168·1	20·8	52·3	3,765
17–18 ,,	145·2	194·6	18·1	54·1	4,090
24–25 ,,	167·2	—	18·6	41·8	3,820
3–4/iv	90·5	123·2	17·2	51·8	3,850

First, we may notice the great difference between the amounts of sugar when determined by the polarimeter and by the reduction of Fehling's solution. No doubt the value as found by Fehling's solution is slightly too high, owing to the presence of small amounts of substances other than glucose which reduce alkaline copper solutions. The value found by the polarimeter is too low, on account of the large quantity of the laevorotatory oxybutyric acid present in the urine. In a very acid urine such as this most of the oxybutyric acid would be present in the free condition (see Table, p. 389); assuming all the acid to be free we obtain on recalculating the polarimeter result for 17–18/ii 148·7 grm. instead of 117·5 grm. of glucose, so that the difference between the two determinations is now only 14 grm. instead of 45 grm., or expressed as a percentage the difference is under a third of one per cent. Thus the reduction value must be pretty near the true value. Suppose the true value for 17–18/ii to be 160 grm. : then since W. M. G. was on a carbohydrate free diet this sugar must be derived from protein or fat or both. Taking the 17·7 grm. of urinary nitrogen as representing the protein decomposed, this would correspond to $\frac{53}{16} \times 17\cdot7 = 58\cdot6$ grm. of protein carbon. But 160 grm. of glucose contain 64 grm. of carbon, so that if all the carbon of the protein decomposed had been converted into sugar it would still be insufficient to account for the amount of sugar excreted. Part of the protein carbon must certainly be excreted as carbon dioxide, another part as urea, and yet another part as the four-carbon-atom acids of the urine and as acetone of the breath. In other words, the conclusion that some sugar is formed from fat in a case such as this seems inevitable.

Unfortunately the acetoacetic acid excreted was not determined; but from the table on page 393 it is pretty certain that it would not be less than 30 per cent. of the oxybutyric acid—that is, on 17–18/ii W. M. G. excreted 68·2 grm. of oxybutyric acid and 20·5 grm. of acetoacetic acid. These amounts of acid contain 41 grm. of carbon. So we have on 17–18/ii :

<div style="text-align:center">

Carbon excreted as glucose . . . 64 grm.

,,   ,,   acids . . . 41 ,,

105 ,,

</div>

To this must be added the carbon of the expired carbon dioxide, of the expired acetone, of the urea and other organic compounds in the urine. Regarding only the carbon dioxide this may be estimated for a man of 8 st.

(51 kilos) at 130 grm., for Benedict and Joslin (45) have shown that the severe diabetic excretes without food 3·31 c.c. of carbon dioxide per kilo of body weight per minute. W. M. G. therefore excreted considerably more than 235 grm. of carbon on 17–18/ii, and as we have seen, his protein carbon only amounted to 58·6 grm.—leaving 176·4 grm. of carbon to be derived from fat. This amount of carbon is contained in 230 grm. of fat. The conclusion at which I arrive from the consideration of this case is that even in the severest type of diabetes carbohydrate is essential, and that protein corresponding to 18 grm. of nitrogen is too small an allowance. In view of the experience gained during the course of this work a more suitable diet for this case would appear to have been one containing something like 100 to 120 grm. of carbohydrate, 20 to 25 grm. of nitrogen in the form of protein, and some 220 grm. of fat—giving, if we take the upper figures, about 300 grm. of carbon and 3,180 calories. For comparison with a case in which the diet was known we may take Case V, P. B., on 22/iv/14, and on 16/v/14 at the end of a vegetable period :

	22/iv/14 (55·8 K.).			16/v/14 (52·2 K.).	
	Grm.	Carbon (grm.).		Grm.	Carbon (grm.).
Sugar	197·9	79·2		36·2	14·5
Acetoacetic	12·9	6·1		4·9	2·3
Oxybutyric	44·0	20·3		16·1	7·4
Expired CO_2	—	142·4		—	133·3
	Total	248·0			157·5
	Total in diet	327·9 = +79·9		Total in diet	123·0 = −34·5

So that on the first of these two days P. B. was overfed as regards fat, perhaps slightly overfed as regards protein, and underfed as regards carbo-hydrate. But on the second day, remembering that the breath carbon is the average figure for severe diabetics without food, and that the total carbon does not include the breath acetone, the urea &c. of the urine, and that a portion of the food carbon would not be assimilated it seems absolutely certain that P. B. was underfed in every way.

The patient W. M. G. died in coma a short time after these determinations were made.

Case VII. W. S. Boy, aged 14 years.

Admitted 10/v/13 to Matthew Ward under Dr. Tooth, C.M.G. Had been treated at the hospital just one year before, also for diabetes. There was no family history of diabetes and the patient's organs were apparently sound.

On 10/v he was very drowsy, his breath smelled strongly of acetone, and his pupils were dilated. He was given 20 grm. bicarbonate of soda every two hours, also 2 oz. per rectum every four hours ; oxygen was also administered. He vomited. On 11/v he was better ; but the breathing was still deep and he was cyanosed. One pint of saline solution and 2 oz. of bicarbonate were given by infusion, and during the progress of this operation the breathing became shallower and the patient's colour improved. He vomited again.

On 12/v he was much better. The breath still smelled of acetone. He was now given 40 gr. of bicarbonate every four hours. These details are given to show how very near the boy was to passing into coma and also to draw attention to the fact that the diet was quite free from carbohydrate. After this vegetables were added to the diet and subsequently some white bread was allowed.

The determinations were begun on 26/vi/13 ; but as the diet was not sufficiently quantitative I have not drawn the curves.

The weight of the patient varied as follows :

Date.	Stones.	Kilos.
10 and 18/v	4 st. 13 lb.	31·3
24/v	5 ,, 2 ,,	32·7
1/vi	5 ,, 2·5 ,,	32·9
8 ,,	5 ,, 1 ,,	32·3
15 and 22/vi	5 ,, 0·5 ,,	32·0
28 ,,	4 ,, 13·5 ,,	31·5
13/vii	4 ,, 12·5 ,,	31·1
19 ,,	4 ,, 13·5 ,,	31·5
27 ,,	5 ,, 1·5 ,,	32·4
3 and 10/viii	5 ,, 3·5 ,,	33·3
17 ,,	5 ,, 4·5 ,,	33·8
23 ,,	5 ,, 6·0 ,,	34·5
1/ix	5 ,, 7·0 ,,	34·9

A von Noorden oatmeal diet was attempted on 28/vi. The result is given in the Table :

Date.	Vol. c.c.	Sugar (grm.) Titration.	Nitrogen (grm.).	Acetone (grm.) by Folin.	Acetoacetic (grm.) by M-K.	Oxybutyric (grm.) by rotation.
26/vi	2,330	100·0	17·6	0·56	8·9	25·1
27 ,,	2,210	76·0	18·3	0·77	7·8	—
28 ,,	1,360	25·0	6·9	0·38	3·9	12·1
29 ,,	1,600	1·3	15·7	0·19	3·4	—
30 ,,	2,530	153·8	8·0	0·62	6·6	20·0
1/vii	3,080	224·8	8·3	0·45	8·0	23·1
2 ,,	2,130	141·4	6·9	0·49	5·2	17·1
3 ,,	1,350	85·1	5·4	0·35	4·3	13·2
4 ,,	1,830	42·5	9·5	0·19	1·8	6·1
5 ,,	1,820	8·4	7·2	0·13	1·8	—
6 ,,	2,530	65·7	17·8	0·27	4·8	15·0
7 ,,	2,100	72·3	17·4	0·59	6·3	19·4
8 ,,	2,460	70·1	21·8	0·65	8·3	24·8
9 ,,	2,800	149·2	18·6	0·34	3·3	8·6

On 30/vi and 1/vii W. S. ate 8 oz. of oatmeal in the form of porridge ; this would contain 147·7 grm. sugar : he also ate on each day twelve oatmeal biscuits, which would contain 64·6 grm. sugar—giving a total for each day of 212·3 grm. This amount of sugar and more is excreted if we include 2/vii as still under the influence of the two preceding oatmeal days. As regards the four carbon atom acids, they are far higher during these three days than one would expect them to be : this may be due to the greatly increased volume of urine. In any case this typical von Noorden treatment must be regarded as an utter failure with respect to W. S. Other cases have been published where the administration of large amounts of oatmeal has increased the amount of acetoacetic acid derivatives excreted. Thus Lipetz (46) gave a woman 32·4 kilo, a severe diabetic : Bouillon, meat, eggs, butter, bread, milk, vegetables, wine, coffee for three days ; oatmeal (almost same amount as W. S.), roborat, butter, wine for three days ; meat, butter, bread, milk, vegetable, wine, coffee for two days, and obtained the following results :

Date.	Vol. c.c.	Sugar (grm.).	FeCl₃.	Acetone (grm.).	Oxybutyric (grm.).
21/i/04	1,700	80·7	weak	—	—
22 ,, ,,	1,275	49·0	weak	—	—
23 ,, ,,	1,550	41·8	+	1·3	3·3
24 ,, ,,	2,000	90·0	+	2·2	7·2
25 ,, ,,	2,550	122·4	+ +	—	—
26 ,, ,,	4,600	170·2	+ +	4·2	16·5
27 ,, ,,	2,150	75·2	+	1·9	5·6
28 ,, ,,	1,500	40·5	+	—	—

The effect of the oatmeal in this case is exceedingly similar to that in the case of W. S.; but here on the next day, 29/i, the patient became comatose and

died.   In another case, not so severe, he obtains a slight diminution of acetoacetic
derivatives.   In yet another case, in which he had reduced the sugar from 144 to
7 grm. by dieting, the patient became free from sugar during the von Noorden
treatment ; but on returning to ordinary diet strong glycosuria occurred : then,
this having been reduced and the oatmeal treatment adopted again, it was
accompanied by fairly strong glycosuria.   In some cases Lipetz finds that the
oatmeal is badly resorbed, undergoes fermentation, and leads to a large increase
in the number of faecal bacteria ; but in the first case quoted this was not so.
In other cases the oatmeal cannot be taken, or if it is there is vomiting : it will
be remembered that W. H. R. could not take the prescribed amount of oatmeal.

      After the von Noorden treatment W. S. was allowed a little carbohydrate—
1 oz. of potato, apples, and vegetable ; and on 9/vii he was given jelly and
stewed apples.   From this point his weight begins to rise steadily to 1/ix, when
he was discharged 'improved' and having gained 3·6 kilos in weight (8 lb.).
In respect of the excretion of the four carbon atom acids he was not improved,
but his diet was such that he could tolerate them better, and no doubt by
a careful increase of a suitable carbohydrate the amount of acid excreted could
have been reduced.   The acetoacetic acid percentage for this case has been
worked out and will be found included in the Table on p. 393 ; the low value of
the ratio at oxybutyric acid 5 to 9·9 grm. is due to the fact that these values are
obtained at the end of the von Noorden period, after an increase of carbohydrate
(9/vii), and after a retention (or a loss ?) of urine.

      In this case the acetone was determined by the method of Folin (47) every
day in addition to the usual Messinger-Huppert.   As is seen from the tables the
total free acetone only exceeded a gram on four occasions out of forty, and these
were no doubt due to the urine standing before the determinations were made.
The result of the Messinger-Huppert determinations is given throughout as
acetoacetic acid.   It will be noticed that the free acetone is always one-tenth or
less than one-tenth of the acetoacetic acid.   Now it is certain that the free
acetone in all these determinations is considerably above the real amount of free
acetone of newly formed urine—that is to say, nearly all the acetone determined
was formed from acetoacetic acid : for the samples of urine were collected from
6 a.m. to 6 a.m., brought to the laboratory about 9.30 a.m., and analysed the
same day if possible.   To show how the acetoacetic acid changes I give an
example—30/v/13 was a hot day and the laboratory temperature was 24° C :
the urine of the patient J. F. was examined for free acetone by Folin's method at
10.30 a.m., and again after standing in the laboratory at 6.10 p.m. ; the results
for the total free acetone were 0·293 and 0·483 grm. respectively.   These
determinations were made with the utmost care so as to be certain that they
were comparable.   The increase of free acetone is 64·8 per cent.   The first to
show that practically all the 'acetone' in diabetic urine is present as acetoacetic
acid was Arnold (48).   Papers confirming him were published by Embden and
Schliep (49), and Folin (47) almost simultaneously.   No author, so far as I am
aware, has published a long series of observations on one and the same patient.

      Appended are the figures for this case from 10/vii to 4/viii.

	Vol. c.c.	Sugar (grm.) by Rotation.	by Titration.	Nitrogen (grm.).	Acetone (grm.) by Folin.	Aceto-acetic Acid (grm.).	Oxybutyric by Rotation.	Acid (grm.) by Titration.
10/vii/13	2,660	82·0	90·3	17·5	0·37	6·3	17·0	18·7
11 ,, ,,	2,220	86·0	93·2	17·8	0·53	6·5	19·1	22·1
12 ,, ,,.	3,050	119·9	121·7	23·7	0·87	8·7	—	—
13 ,, ,,	2,520	106·0	101·6	21·2	0·78	9·9	25·1	28·2
14 ,, ,,	1,330	48·5	47·4	13·5	0·55	5·2	14·3	15·5
15 ,, ,,	2,450	103·6	116·2	17·9	0·72	8·7	24·4	27·8
16 ,, ,,	1,940	68·9	79·9	14·4	0·78	7·9	20·8	23·0
17 ,, ,,	2,440	69·0	81·0	18·4	0·64	9·6	32·2	33·1
18 ,, ,,	2,440	—	97·8	20·9	0·86	9·4	26·3	27·2
19 ,, ,,	2,560	—	102·9	20·5	1·10	11·0	—	—
20 ,, ,,	1,650	—	63·0	16·9	0·72	7·1	22·0	23·7
21 ,, ,,	1,980	—	90·2	18·4	0·73	8·0	22·7	23·0
22 ,, ,,	2,060	—	69·2	14·2	0·55	7·0	24·1	25·0
23 ,, ,,	2,620	—	92·7	17·1	1·04	11·5	34·3	34·8
24 ,, ,,	2,020	—	48·5	14·0	0·78	7·4	22·6	22·8
25 ,, ,,	1,470	—	56·0	11·7	0·31	3·3	9·0	8·7
26 ,, ,,	2,140	—	90·7	14·6	0·65	7·4	—	—
27 ,, ,,	2,040	—	90·8	14·9	0·62	8·3	24·0	25·7
28 ,, ,,	2,480	—	105·9	19·4	0·92	10·1	28·2	26·2
29 ,, ,,	1,880	—	66·0	16·2	0·55	7·3	21·2	21·2
30 ,, ,,	2,740	—	90·4	19·5	0·87	10·7	29·5	—
31 ,, ,,	1,480	44·7	42·9	11·9	0·49	5·6	12·8	16·2
1/viii/13	3,000	108·5	112·8	20·4	1·04	12·1	34·3	36·7
2 ,, ,,	2,800	74·6	—	21·4	1·45	12·3	23·0	27·1
3 ,, ,,	2,230	69·2	—·	19·2	0·85	8·9	27·2	28·2
4 ,, ,,	2,130	68·8	—	16·2	0·81	9·1	26·5	26·9

The sugar is given both by rotation and titration on several days. The differences shown are quite typical ones and I am unable to give an explanation that will hold in every case, and the subject is too complicated to discuss in this paper; I draw attention to them because they show the futility of attempting to draw conclusions as to the amount of oxybutyric acid present in a urine from the two values for the sugar except where the difference between them is very great, as in the case of W. M. G.

The oxybutyric acid is also given as determined by rotation and titration; the small differences show two important points, namely, (a) that there can be practically no dextro-rotatory oxybutyric acid in this urine, (b) there must be very little of any other acid soluble in ether present in the urine. Further, the longer a urine stands before these determinations are made the greater the difference becomes, because acids are formed by fermentations occurring in the urine.

DISCUSSION OF RESULTS.

The Production of the Four Carbon Atom Acids of Diabetic Urine.

Külz (1) thought it possible that the acid which he discovered in certain diabetic urines, his pseudo-oxybutyric acid, was a normal oxidation product of glucose. Hugounenq (50) also thought it might be formed from glucose, in some such way as the following:—alcohol might first be formed from glucose as it is formed from this substance by yeast, and alcohol is known to be

oxidized by the body to aldehyde; the latter might undergo the aldol condensation, and aldol on oxidation would give oxybutyric acid.

$$
\begin{array}{ccccccc}
 & & & & CH_3 & & CH_3 \\
 & & & & | & & | \\
CH_3 & \rightarrow & CH_3 & \rightarrow & CHOH & \rightarrow & CHOH \\
| & & | & & | & & | \\
CH_2OH & & CHO & & CH_2 & & CH_2 \\
 & & & & | & & | \\
 & & & & CHO & & COOH
\end{array}
$$
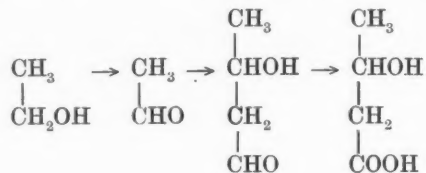
He says, 'It must however not be forgotten that the chemistry of living beings differs from the chemistry of the laboratory rather in its methods than in its results, and that general chemistry often endeavours to attain by drastic reactions (*reactiones brutales*) what biological chemistry on its part accomplishes by delicate but still unknown processes.'

Magnus-Levy (6) discusses the origin of hydroxybutyric acid by synthesis. He states that molecules of compounds containing three atoms of carbon are at the disposal of the body—such are glycerine and lactic acid; and he refers to the well-known formation of butyric acid from lactic acid by bacterial action. According to a verbal communication made to him by Spiro this conversion can be conceived of as happening by the resolution of lactic acid into aldehyde and formic acid, the former condensing to crotonic aldehyde which then adds on hydrogen and oxygen to form butyric acid.

$$
\begin{array}{ccccccc}
CH_3 & & & & CH_3 & & CH_3 \\
| & & & & | & & | \\
CHOH & \rightarrow & CH_3 & \rightarrow & CH & \rightarrow & CH_2 \\
| & & | & & \| & & | \\
COOH & & CHO & & CH & & CH_2 \\
 & & & & | & & | \\
 & & & & CHO & & COOH
\end{array}
$$
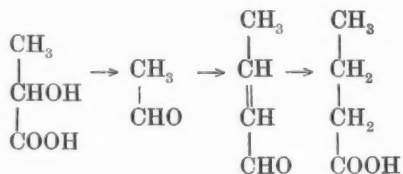
If, before the formation of butyric acid is completed, a further oxidation happens, one arrives quite easily according to Spiro at oxybutyric acid.

The view that the four carbon atom acids of diabetic urine are derived chiefly from sugar has long been abandoned; but no one denies that sugar is a main source of such lactic acid as is found in the tissues and urine. If aldehyde were shown to be produced from lactic acid in the body then hydroxybutyric acid or more probably acetoacetic acid might be produced from it by the series of reactions suggested by Hugounenq. (See below.)

Minkowski (27) was the first to suggest that hydroxybutyric acid was derived from fat or from amino-acids. At the present time most observers regard fat as the chief source of both acids, while protein is regarded as a source of a smaller part of the acids.

We will first consider the origin of the four carbon acids from fat.

A. *By feeding with fat.* Experiments have often been made with the object of showing the production of 'acetone' by administering large quantities of

fat to man. The results of such experiments are singularly disappointing.
A normal man does not produce 'acetone' on a diet rich in fat if the diet
contains a moderate amount of carbohydrate: therefore in his case the experi-
ments must be made with carbohydrate free diets. The disappointing feature
in all such experiments is the entire want of proportion between the quantities
of fat administered and the quantity of 'acetone' produced. I give a few
results.

Rosenfeld (51), in a paper which summarizes his own work and that of some
of his pupils, states: 'Fat has only an action on acetonuria in so far as it
influences the causal factor of acetonuria—the decomposition of protein.' No
doubt Rosenfeld is incorrect in regarding protein as the only source of 'acetone';
but his experiments must be taken as correct, their chief defect being their
short duration :—

	Nitrogen grm.		Acetone mg.	
R. fasting excreted	6·4		32	
R. on 92 grm. of butter alone excreted . . .	9·3		63	
O. fasting excreted on 2 days	13·7	12·9	90·9	310
O. on 190 grm. of butter alone, excreted on 2 days .	13·1	11·9	82·3	236

Some results of Hirschfeld have been given on page 336. They show very
clearly the difficulty of drawing satisfactory conclusions from experiments of
this kind.

The following results of Geelmuyden (52) are of special value because they
were made on healthy medical students; all of practically the same age, 20 to
21·5, and differing little in weight, 68 to 75 k., and the fat given was almost
entirely butter fat; moreover he usually determines the fat in the faeces.

	Day.	Fat (grm.).		Nitrogen (grm.).	Acetone (mg.).
		Food.	Faeces.		
i	1	249	7·7	30·6	116
	2	469	40·0	25·0	370
	3	29	17·7	27·3	144
	4	42	—	30·7	78
ii	1	138	16·3	31·9	33
	2	239	18·4	32·7	244
	3	110	—	17·8	95
	1	288	—	24·4	276
	2	291	4·9	20·5	302
	3	34	9·5	18·3	370
	4	27	21·5	19·3	396
iv	1	39	4·2	29·8	72
	2	160	—	17·2	171
	3	39	—	21·4	221
v	1	25	6·9	26·4	22
	2	26	—	26·3	46
	3	94	—	—	360
	4	—	5·1	—	—

The table is of great interest because it shows what a minute fraction if any
at all of the fat is converted into 'acetone', also because it shows clearly the
variation from one individual to another, and lastly because the value on any
one day is considerably below that found by Fr. Müller in the cases of the

professional fasting men, Cetti (784 mg. on the fourth day of hunger), and Breithaupt (575 mg. on the fifth day of hunger).

Schwarz (53) regards the appearance of 'acetone' as the sign of an abnormal decomposition of fat. In normal men he fails to produce more than a minute increase of the acetoacetic acid by adding fat to the diet, and he shows that even this is not always obtained. As regards the diabetic Schwarz is a little, but a very little, more fortunate : three examples may be given ; all are described as severe diabetics, the figures are the average for the days stated, and all the acetoacetic acid derivatives are expressed as oxybutyric acid so that the figure includes the acetone of the breath as well as the substances usually determined.

Days.	Daily fat.	Acetoacetic derivs. as oxybutyric acid.	Remarks.
i–ii	—	2·5 grm.	Man, aged 26.
iii–iv	200 grm. Lard	3·7 ,,	
v–vi	—	3·5 ,,	
vii–viii	200 grm. Butter	4·6 ,,	
i–viii	—	19·2 ,,	Man, aged 45.
ix–x	150 grm. Lard	24·2 ,,	
xi–xii	—	21·9 ,,	
xiii	150 grm. Butter	28·0 ,,	
i	—	15·5 ,,	Man, aged 42.
ii	100 grm. Oleic acid	17·0 ,,	

I see no proof in these figures of 'acetone' being formed from fat ; the variations are well within those which may occur in any diabetic. If 200 grm. of butter and 100 grm. of oleic acid can only cause increases of 1·1 grm. and 1·5 grm. of oxybutyric acid respectively they are exceedingly poor acetone formers. The results of Hagenburg (54) have been extensively quoted as proving the origin of 'acetone' from fat ; they are as follows :—

Hunger	97 mg. acetone	
*Butter 262 grm.	186 ,,	,,
Normal food	86 ,,	,,
Hunger	70 ,,	,,
*Butter 110 grm. + Ca-butyrate 12 grm. . .	231 ,,	,,
Normal food	71 ,,	,,
Hunger	100 ,,	,,
Lard 62 grm.	57 ,,	,,

* Contained 2·2 and 0·89 grm. of free fatty acid respectively.

So that 110 grm. of butter and 12 grm. of calcium butyrate give a better yield of acetone than 262 grm. of butter, while 62 grm. of lard actually depress the excretion of acetone !

Mohr and Loeb (55) claim to have shown in the case of a diabetic patient (evidently a slight case) almost an exact parallelism between the acetone body excretion and the fat in the patient's food, and in the same patient they demonstrated in a way, which they say 'cannot be doubted', a direct formation

of oxybutyric acid from butyric acid. This is done as follows : The patient, aged 19, has a diet of 500 grm. of meat, vegetables four times a day ; coffee, tea, bouillon, Offenbach water, and addition of fat.

Day.	Added fat, &c.	Sugar grm.	Oxybutyric acid grm.	Total acetone bodies as oxybutyric.
30/xii/01	300 grm. butter	16·2	13·2	18·3
31 ,, ,,	,, ,, ,,	18·6	10·0	16·2
1/i/02	,, ,, ,,	21·3	8·2	14·2
2 ,, ,,	,, ,, ,, +20 grm. NaHCO₃	23·8	4·9	9·0
3 ,, ,,	,, ,, ,, + ,, ,, ,,	16·0	5·2	8·5
4 ,, ,,	,, ,, ,, + ,, ,, ,,	7·1	4·5	7·9
5 ,, ,,	,, ,, ,, +20 grm. butyric acid (per clysma)	7·0	8·0	11·4
6 ,, ,,	,, ,, ,, +16 grm. (approx.) butyric acid (per clysma)	6·0	14·0	19·0
7 ,, ,,	,, ,, ,, +20 grm. butyric acid (per os)	9·0	12·7	17·8

The butyric acid was neutralized by NaHCO₃.

Loeb now averages 2, 3, and 4/i, and 5, 6, and 7/i, and concludes that the 56 grm. of butyric acid are responsible for an increase of 19·5 grm. of oxybutyric acid. I fail entirely to see why Loeb takes no account of 30, 31/xii and 1/i, when the total acetone bodies are higher by a little than they are during the butyric acid period. Unless Loeb is prepared to prove that a daily dose of soda of 20 grm. reduces the acetone body excretion in the remarkable way shown by these figures I am not prepared to accept his results as proving the origin of oxybutyric acid from butyric acid.

Some remarkable experiments of Schuman-Leclercq (56) on himself must also be referred to ; they are in two sets, the determination of the breath acetone being omitted in the first set and undertaken in the second. In neither set does he obtain a ferric chloride reaction in the urine on any occasion ; this fact alone shows that he can never have produced more than a small amount of aceto-acetic acid. His results are as follows for the first set of experiments :—

	Acetone mg.	
	Lowest.	Highest.
13 days on mixed diet	2·0	17·0
25 days on black coffee, and meat with the sole addition on certain days of sodium bicarbonate ; sugar by mouth ; sugar by rectum ; laevulose	32·0	194·0
1 day—the next after the meat diet ; on 600 grm. of butter only	83·0	83·0
1 day—next after the butter ; on mixed diet . . .	23·0	23·0

After four days on mixed diet followed by one day of fasting he takes 500 grm. of butter only on one day and obtained 14 mg. acetone ; and the day after this he takes (300 grm. butter + 200 grm. goose fat + 40 grm. laevulose per rect.) and obtains 39 mg. acetone.

From the second set of experiments I make the following summary :—

	Urine.	Acetone mg. Breath.	Total.
16 days mixed diet. Highest	18	0	18
4 days meat only. Highest (second day)	186	55	241
5 days mixed diet. Highest	21	0	21
Next day 272 grm. butter only	30	0	30
„ „ 272 grm. butter + 350 grm. maize bread	19	120	139
„ „ 272 grm. butter + 350 grm. maize bread	6	241	247
„ „ 272 grm. butter only	18	18	36
„ „ mixed diet	15	506	521
„ „ mixed diet	6	0	6
5 next days mixed diet. Highest	24	9	33
Next day, fast	127	18	145
„ „ fast	152	672	824
„ „ fast 0·5 kilo sauerkraut.	535	288	823

The mere act of fasting produces far more acetone than any quantity of fat which Schuman-Leclercq took ; and on the only day when one would be inclined to say that acetone was produced from fat the supposed acetone (506 mg.) is practically all contained in the breath. I think it highly probable that this was not all acetone but contained some aldehyde.

The only other experiments of this kind that need be referred to are those of Joslin (57). In these the fat of the faeces was determined and the acetone of the breath; they were all done on the same healthy man. Here again only minute increases of total 'acetone' compared with the amount of substance catabolized were established, and in some cases there were actual decreases in the total 'acetone': thus 104 grm. of oleic acid given on the second day of fasting caused an increase of 305 mg. of acetone. 74 grm. on another occasion gave 873 mg.: 104 grm. of stearic acid, 59 of triolein, and 104 grm. of butyric acid caused decreases of 234, 52, and 65 mg. respectively.

Thus the direct proof that acetoacetic acid and its derivatives are formed from fat fails completely.

B. *Perfusion experiments.* A method of proving that acetoacetic acid and acetone may be formed from fat or rather from fatty acid is to be found in the experiments of Embden and his collaborators. In these experiments the freshly excised liver of a 6 to 9 kilo dog is perfused usually with 1,600 c.c. of ox blood at a temperature of 40° C. for 75 to 90 minutes. An aliquot part of the perfused blood is freed from protein by precipitation with acid mercuric chloride (Schenck), and one part of the filtrate is distilled to determine total 'acetone' after the Messinger-Huppert method and another part is freed from acetone as such by distillation under reduced pressure, then distilled under ordinary pressure to determine the acetone from acetoacetic acid (49). When blood alone is used from 12 to 27 mg. of total acetone per litre of blood are obtained: of this amount about 90 per cent. is in the form of acetoacetic acid (58). The following are very important points in regard to these experiments: (*a*) The blood used must be thoroughly aerated during the whole time of the experiment. (*b*) The liver must be quite freshly excised. (*c*) No increase in the yield of acetone is obtained by prolonging the experiment beyond the time stated above. (*d*) It was shown that acetone is formed in these experiments by concentrating

the acetone by successive distillations and preparing from the concentrated acetone a derivative—dibenzal-acetone—and taking its melting-point.   The yield of this derivative was far below the yield calculated from the result of the Messinger-Huppert process.   This seems to indicate that other iodoform-producing substances besides acetone are obtained.   In fact Blum and Koppel (59) have definitely proved this for one case.   (e) Embden and his fellow workers have never given a direct proof of the presence of acetoacetic acid as such in any of their perfusion experiments: they have shown that a substance is produced in these experiments which yields acetone on distillation and they have assumed that this substance is acetoacetic acid.   As far as their experiments go the mother substance of the acetone might be acetone-dicarboxylic acid, which also yields acetone and carbon dioxide on distillation and gives a violet red colour with ferric chloride:

$$
\begin{array}{ccc}
\text{COOH} & & \\
| & & \\
\text{CH}_2 & \text{CH}_3 & \text{CH}_3 \\
| \rightarrow & | \rightarrow & | \\
\text{CO} & \text{CO} & \text{CO} \\
| & | & | \\
\text{CH}_2 & \text{CH}_2 & \text{CH}_3 \\
| & | & \\
\text{COOH} & \text{COOH} &
\end{array}
$$

Acetone-dicarboxylic acid
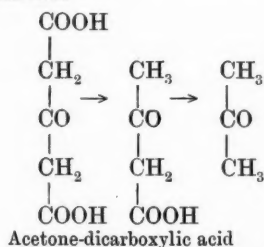
(f) Embden and his colleagues could not isolate hydroxybutyric acid in any of these experiments.

When butyric acid and many acids having an even number of carbon atoms above it in the acetic acid series are neutralized by ammonia and added to the perfusion blood, iodoform-producing substances are always formed on perfusion through a freshly excised liver.   Assuming that acetone is the only iodoform-yielding substance obtained in such experiments, and taking the maximum yields obtained by Embden, Salomon, and Schmidt (60) for butyric acid and by Embden and Marx (61) for n-caproic (C_6), n-octylic (C_8), and n-decanoic (C_{10}) acids, the results were respectively 18, 17·8, 11·9, and 16·9 per cent. of theory.   Acetone was definitely proved by the dibenzalacetone method in the case of butyric acid, the usual bad yield being obtained, but I do not gather that this was done for the other acids.   The acids of the acetic series which had an odd number of carbon atoms do not yield these large amounts of iodoform-producing substances.   Here then we have proof that under certain circumstances acetone and very probably acetoacetic acid may be produced from the fatty acids of the acetic series having an even number of carbon atoms.

C. *Oxidation of fatty acids by hydrogen peroxide.*   Another method of proving that acetoacetic acid and acetone may be derived from fatty acids is due to the very valuable work of Dakin.   He showed that a large number of the fatty acids of the acetic acid series, and many derivatives of these acids also, could be oxidized by acting upon the ammonium salt of the acid in aqueous solution with 3 per cent. hydrogen peroxide at 37°.   From the

following acids Dakin (62) actually isolated from many other products acetone : normal butyric acid, isobutyric acid, isovaleric acid. From the first of these three acids (63) he was able to show that, when oxidized in this way, a substance giving some of the tests for acetoacetic acid was formed. Caproic acid and the acids above it were incompletely investigated but they were found to yield carbon dioxide, lower fatty acids, acetic aldehyde, and ketones derived from β-ketonic acids (64). E. g.,

$$C_9H_{19}.CH_2.CH_2.COOH \text{ (Lauric acid)}$$

$C_9H_{19}.CO.CH_2.COOH$	$C_nH_{2n+1}.COOH$	$CH_3.CHO$
(the β-ketonic acid)	Lower fatty acids	Acetaldehyde
	n being less than 11	

$$C_9H_{19}COCH_3$$
Methyl-nonyl-ketone
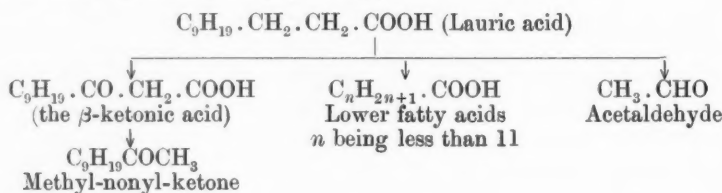
In this way then it has been shown that a few lower fatty acids yield acetone on oxidation and one, namely butyric acid, yields acetoacetic acid, while the most obvious product of the oxidation of the higher fatty acids appears to be a higher ketone ; certain of these higher ketones are in fact found in plants, but none has been found so far in the animal body. Dakin could not find hydroxybutyric acid among the oxidation products of butyric acid (63). It may be mentioned that Neubauer (65) claims to have proved the production of β-hydroxybutyric acid from butyric acid by oxidation with potassium per-sulphate : from 37 grm. of sodium butyrate, by leaving it for some days with a solution of 90 grm. of the persulphate, removing excess of butyric acid, and distilling with concentrated sulphuric acid, he obtained a ' Spärliche Menge ' of crystals which from their appearance, smell, melting-point (69° instead of 71°), and ability to blacken osmium tetroxide, he concluded must be crotonic acid. (No analysis.)

D. *From the quantity of the four carbon atom acids found in diabetic urine.* It has been shown in the case of W. M. G. that if all the urinary nitrogen on a certain day be regarded as derived from the catabolism of protein the latter would contain 58·6 grm. of carbon. Now the four carbon atom acids and acetone excreted on the same day contained 41 grm. of carbon. Since much of the sugar excreted which contained 64 grm. of carbon must be supposed to arise from protein, the rest of these must be derived from fat or from sugar.

I take a case of Joslin's (66) which yielded the most remarkable figures of any case I have met with in the literature, and give the carbon equivalents for three successive days during coma :

N.	*Acids + Acetone.*	
61·3	40·0	
78·8	71·2	Carbon equivalents.
61·9	54·4	

On the second and third of these days, and on the same assumption as before that the nitrogen represents protein catabolized, if any considerable part

of the protein carbon has contributed to the production of sugar, and the sugar excreted on these days corresponded respectively to 93 and 24 grm. of carbon, then a large part of the acids and acetone must be derived from fat or sugar.

In Magnus-Levy's girl (10), aged 12, we have on 23–24/ii/99,

N.	Acetoacetic acid.	Oxybutyric.	
70·9	12·4	37·5	. Carbon equivalents.

Here the protein carbon is far more than sufficient to account for the acid and acetone carbon—there is an excess of 21 grm. of protein carbon which would correspond to 52·5 grm. of sugar. On the same day the child excreted 284 grm. of sugar and took about 4 litres of milk = 180 grm. of sugar.   In this case indeed the protein catabolism is such that it could account quite well for a large part of the four carbon atom acids.

From the statements of fact under A, B, C, and D the writer would be inclined to the view that a considerable proportion of the four carbon atom acids of the urine, of the trace of urinary acetone, and of the breath acetone, is derived from fat, but the evidence does not warrant the conclusion that fat is such an important source of those compounds that the other two components of a diet are negligible as a source in comparison with it.

The Mode of Origin from Fat.

One of the difficulties as regards the processes referred to under B and C is that the one acid which yields per grm. by far the most acetone, is the one which forms by far the smallest percentage of the fatty acids which compose the fats commonly eaten as food, namely butyric acid. This acid only occurs in butter fat and only forms about 5 per cent. of that substance. Not only so, but the diabetic patient can and does form large quantities of the four carbon atom acids when he is deprived of butter. The tissue fat of the diabetic is no richer in lower fatty acids than normal fat, nor has it a different iodine number, that is, it is not more unsaturated : in a specimen of fat from a fatal case of diabetic coma I found a Reichert-Wollny number of 0·4 and an iodine number of 48·9 ; and these are normal values. If the fat given to a diabetic who is producing large quantities of the four carbon atom acids does not contain butyric acid, and if his tissue fat does not contain it, how are these derivatives of butyric acid to be accounted for ? It is usually supposed that since these pathological acids may be regarded chemically as derivatives of butyric acid they must necessarily be derived from butyric acid in the body. So it was desirable to show how a high fatty acid could be broken down in such a manner as to produce butyric acid. Knoop (67) was the first to do this ; he observed that by rendering an easily oxidizable substance less easily oxidizable by substituting a group difficult of oxidation for one easily oxidized, in such a way as to keep the general character of the substance the same, information might be obtained as to the intermediate oxidation products.

Accordingly Knoop studied the oxidation in the animal body of certain phenylated fatty acids. Phenylacetic acid was known not to be oxidized, but to combine with glycocoll and to be excreted as phenaceturic acid.

Phenylpropionic acid was known to undergo oxidation and to yield benzoic acid which was excreted as hippuric acid. Now if phenylpropionic acid first produced phenylacetic acid, the latter would be excreted as phenaceturic acid. Knoop therefore inferred that phenylpropionic acid undergoes oxidation at the β-carbon atom and not at the a-carbon atom. To confirm this theory of β-oxidation he gave phenylbutyric and phenylvaleric acids to a dog and observed that the former acid was oxidized to phenylacetic acid and excreted as phenaceturic acid, while the latter was oxidized probably to phenylpropionic acid first, then to benzoic acid, and was therefore excreted as hippuric acid :

$$\overset{\beta}{C_6H_5.CH_2.CH_2}\overset{a}{.CH_2}.COOH$$
Phenylbutyric

$$\overset{\beta}{C_6H_5CH_2.CH_2.CH_2}\overset{a}{.CH_2}.COOH$$
Phenylvaleric

$$C_6H_5CH_2COOH$$
Phenylacetic

$$C_6H_5CH_2CH_2COOH$$
Phenylpropionic

$$C_6H_5COOH$$
Benzoic
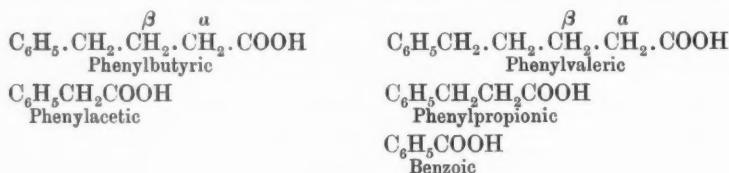
From this it is clear that a normal dog breaks down the phenylated fatty acids by removing two carbon atoms at a time from the carboxyl end of the chain until the acid containing an even number of fatty acid carbon atoms reaches phenylacetic acid or one containing an odd number reaches benzoic acid. But the oxidation of these acids is not so simple as it appears from the scheme just given. We owe the further elucidation of the changes that occur in this process to Dakin. He showed that when phenylpropionic (68), phenylbutyric (69), and phenylvaleric (70) acids are given subcutaneously to animals (cats and dogs) many intermediate substances could be isolated, namely :

1. $C_6H_5.CHOH.CH_2.COOH$ — β-hydroxyphenyl-propionic acid
2. $C_6H_5.CO.CH_2.COOH$ — Benzoylacetic acid
3. $C_6H_5.CH:CH.COOH$ — Cinnamic acid *
4. $C_6H_5.CO.CH_3$ — Acetophenone
5. $C_6H_5.COOH$ — Benzoic acid *

From $C_6H_5CH_2CH_2COOH$ Phenylpropionic acid

6. $C_6H_5.CH_2.CHOH.CH_2.COOH$ — β-hydroxyphenyl-butyric acid
7. $C_6H_5.CH_2.COOH$ — Phenylacetic acid

From $C_6H_5CH_2CH_2CH_2COOH$ Phenylbutyric acid

1, 3, 4, 5

From $C_6H_5CH_2CH_2CH_2CH_2COOH$ Phenylvaleric acid

* Excreted in combination with glycocoll.

These results of Dakin confirm and greatly amplify those of Knoop ; they also furnish an explanation of the results obtained by Embden on the perfusion

of a surviving liver with blood to which a salt of butyric acid has been added; and finally they are in line with Dakin's observations on the oxidation of butyric acid with hydrogen peroxide except in respect of the formation of the hydroxy-acids.   But the writer is of opinion that they do not justify the theory of β-oxidation as enunciated by Knoop.   On this theory butyric acid is oxidized by attack at the β-carbon atom only, forming the hydroxy-acid, which is then oxidized to the ketonic acid.   Friedmann (71) first attacked Knoop's theory on the ground that in purely chemical reactions only the a-carbon atom proves capable of entering into reaction in the normal fatty acids, but he appears to have withdrawn his objection at a later date (72).   My own objection to the theory is that in a fatty acid a single carbon atom is never attacked, but that when attack does take place two adjacent carbon atoms are involved— in the case of a fatty acid the a- and β-carbon atoms first.   The production of a-halogen fatty acids alone, e.g. $CH_3.CHBr.COOH$ only occurs when the hydroxyl group has been replaced by halogen.   I should therefore explain the oxidation of the fatty acids as happening as follows, using butyric acid as an example:

I.

$$
\begin{array}{ll}
CH_3 & CH_3 \\
| & | \\
CH_2+O = & CH+H_2O \\
| & \| \\
CH_2 & CH \\
| & | \\
COOH & COOH \\
& \text{Crotonic acid}
\end{array}
$$

II.

$$
\begin{array}{ll}
CH_3 & CH_3 \\
| & | \\
CH+O = & CH \\
\| & |>O \\
CH & CH \\
| & | \\
COOH & COOH
\end{array}
$$

III.

$$
\begin{array}{ccccccc}
CH_3 & CH_3 & CH_3 & CH_3 & CH_3 & CH_3 & CH_3 \\
| & | & | & | & | & | & | \\
CHOH \leftarrow & CO \leftarrow & COH \leftarrow & CH \rightarrow & CH \rightarrow & CH_2 \rightarrow & CH_2 \\
| \ \text{Reduc-} & | \ \rightarrow & \| & |>O & \| & | & \text{Reduc-} \ | \\
CH_2 \ \text{tion} & CH_2 & CH & CH & COH & CO & \text{tion} \ CHOH \\
| & | & | & | & | \leftarrow & | & | \\
COOH & COOH & COOH & COOH & COOH & COOH & COOH \\
& \text{Keto-form} & \text{Enol-form} & & \text{Enol-form} & \text{Keto-form} &
\end{array}
$$

Tautomeric forms of   Tautomeric forms of
Acetoacetic acid a-Ketobutyric acid

It should be observed that since the urinary acetoacetic acid readily gives the

ferric chloride reaction it must be chiefly in the enol-form and not as it is usually written in works on chemical pathology in the keto-form.

This scheme would account for all the products obtained by Dakin by oxidation of butyric acid by hydrogen peroxide—thus his yield of 'about 50 per cent. of theory of acetone' would be explained by assuming that about half of the oxidation product of crotonic acid assumed the form of acetoacetic acid and his propionic aldehyde would be derived from the a-ketobutyric acid 3. Similarly all the products 1, 2, 3, 4, 5 obtained from phenylpropionic acid are easily accounted for, and also the missing part of the administered compound for phenyllactic acid which would be produced is known to be burned in the normal animal body.

The a-ketonic acid would also be able to form an amino-acid, and in fact Kondo (73) has shown that a-ketobutyric acid when perfused through the liver does form a-aminobutyric acid. Embden and Schmitz (74) have shown that other a-ketonic acids also form amino-acids in this way, e. g. phenylpyruvic acid gives phenylalanine. Knoop (75) and Knoop and Kertess (76) showed that a-ketonic and also a-hydroxyacids could produce acylated aminoacids in the organism of the dog:

$$\begin{array}{ccc}
CH_2 C_6 H_5 & CH_2 C_6 H_5 & CH_2 C_6 H_5 \\
| & | & | \\
CH_2 & \rightarrow \quad CH_2 \quad \leftarrow & CH_2 \\
| & | & | \\
CO & CH \cdot NH COCH_3 & CHOH \\
| & | & | \\
COOH & COOH & COOH
\end{array}$$

a-ketophenylbutyric acid $\quad a$-acetylaminophenyl-butyric acid $\quad a$-hydroxyphenylbutyric acid
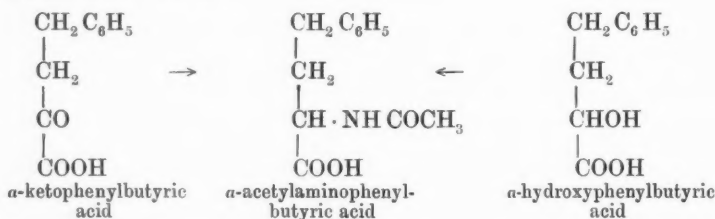
This behaviour of the a-keto acids would account to some extent for a phenomenon observed by many workers on diabetic subjects, namely a retention of nitrogen. For example, Rumpf (77), whose patients were watched day and night, and were not allowed to go for a walk unaccompanied, observed in one case (C. W. 54 kilos) a retention of 9 grm. of nitrogen a day. He asks, Is this nitrogen added on as protein or is there a failure to excrete some nitrogenous end product of metabolism?—and he inclines to the former view. It would also account in part for the retention of nitrogen which is frequently observed in feeding experiments with certain aminoacids. (See below.)

In the above scheme a part of the crotonic acid would undoubtedly be directly oxidized at the double linking before the addition of oxygen could occur, for the $a\beta$-unsaturated acids are known to be very easily attacked at the double linking.

I do not, however, believe that the attack at the $a\beta$-position alone is the only way in which the fatty acids are attacked in the organism, or even the chief way, and my reasons for this statement are as follows: (a) If this were the case the chief fatty acids of the food (oleic, palmitic, and stearic) should give rise to a large amount of a large number of intermediate fatty acids such as

butyric (C_4) caproic (C_6), . . . &c. to lauric acid (C_{12}).   So far as I can see from the literature these acids are not found in the human body.   The supporters of the β-oxidation theory or even of the modified theory suggested above would be compelled in case they regard one or other of them as the only method by which the fatty acids are broken down in the body, to deduce a large part of the oxybutyric acid excreted by the diabetic from butyric acid.   In this case a patient excreting, say 70 grm. a day of this acid must have at any moment a large amount of butyric acid distributed throughout his tissues.   Now both the free acid and its salts have an extraordinarily characteristic smell, and if the acid were present in the amount required to produce these large quantities of oxybutyric acid, even if it were present as a salt, its smell would inevitably reveal its presence.   The breath of a diabetic may smell of acetone, but his body does not smell of butyric acid; the fat from the tissue of the diabetic who died in coma already referred to had no smell of butyric acid: the lipaemic blood of another patient who died in coma had no smell of butyric acid.

(b) It appears probable that the high fatty acids are not merely attacked at the $\alpha\beta$-carbon atoms, that is at the two carbon atoms adjacent to the carboxyl, but at many points in succession along the whole length of the chain, in accordance with the scheme given, forming compounds containing the 'multiple ketene' group of Collie (78)—for example the acid

$-CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot COOH$, would form
$-CO\ \ CH_2\ \ CO\ \ CH_2\ \ COOH$, and
$-CH_2CO\ \ \ CH_2\ CO\ \ COOH$.
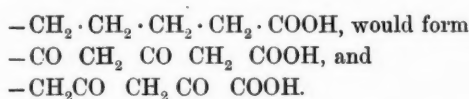
N.B.—The group $-CH_2CO-=-CH=COH-$ is called the ketene group.

Collie points out that such substances very easily lose carbon dioxide, and that they undergo a variety of condensations with extreme ease: he also indicates the possibility of the formation of the sugar grouping from such compounds:

$$
\begin{array}{cccc}
| & | & & | \\
CO & C \cdot OH & & H \cdot C \cdot OH \\
| & \rightarrow\ \| & & | \\
CH_2 & \leftarrow\ CH & \rightarrow & HO \cdot C \cdot H \\
| & |\ \ 2H_2O & & | \\
CO & C \cdot OH & & H \cdot C \cdot OH \\
| & \| & & | \\
CH_2 & CH & & HO \cdot C \cdot H \\
| & | & & |
\end{array}
$$
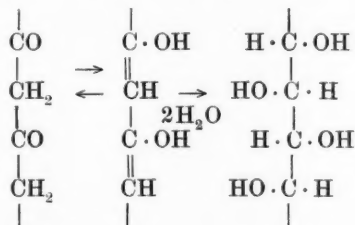
Such a mode of attack of the long fatty acid chains—

(a) would not require the formation of the lower fatty acids, those between butyric and palmitic, which are not found in the human body;

(b) would account for the formation of highly unsaturated fatty acids such as have been found by Leathes (79) and his fellow workers;

(c) would account for the production of such an amino-acid as Fischer and Abderhalden's diaminotrioxydodecanic acid $C_{11}H_{18}(NH_2)_2(OH)_3COOH$;

(*d*) would furnish a simple explanation of the direct formation of aceto-acetic acid without the intermediate formation of oxybutyric acid or aldehyde ;

(*e*) would account for the absence of fatty acids with an odd number of carbon atoms ;

(*f*) would furnish one method of accounting for the small amounts of glyoxylic acid which Dakin (80) found in animal tissues and excretions.

The method of attack indicated is not the only one conceivable. The oxidation of a fatty acid may possibly begin at the methyl end of the chain as well as at the carboxyl end. It will be recalled that in order to isolate inter-mediate products formed in the body from fatty acids the methyl group in these acids had to be replaced by the relatively unattackable phenyl group. I can only find one piece of direct evidence showing that the methyl group can be attacked ; but I believe that such evidence is bound to accumulate. Raper (81) oxidized methyl-butyric acid, by hydrogen peroxide and found amongst the products methyl-succinic acid, clearly showing that in this case the methyl group was attacked.

$$CH_3\ CH_2\ CH\ CH_3\ COOH \qquad\qquad COOH\ CH_2\ CH\ CH_3\ COOH$$

The Origin from Protein.

The food protein is resolved by the digestive ferments completely into its component amino-acids. The latter, as appears both from the work of Folin and Denis (82), (83), and of van Slyke and Meyer (84), enter the blood-stream very rapidly and are presented to the tissues ; these supply their needs from them and the surplus of amino-acids is catabolized. Dakin and Dudley (85) have shown that the first step in the catabolism of an amino-acid is most probably the production of a glyoxal derivative ; and the same two workers have established the existence of an enzyme, glyoxalase, which is present in the blood-cells and in all the tissues of the body except the pancreas, which converts the glyoxal derivatives of the amino-acids into the corresponding *a*-hydroxy acids, e. g.—

$CH_3\ CH_3$	$CH_3\ CH_3$	$CH_3\ CH_3$	$CH_3\ CH_3$
CH	CH	CH	CH
CH_2	CH_2	CH_2	CH_2
$CH\ NH_2$	CO	CHOH	COOH
COOH	CHO	COOH	
Leucine	Isobutylglyoxal	Leucic acid	Isovaleric acid
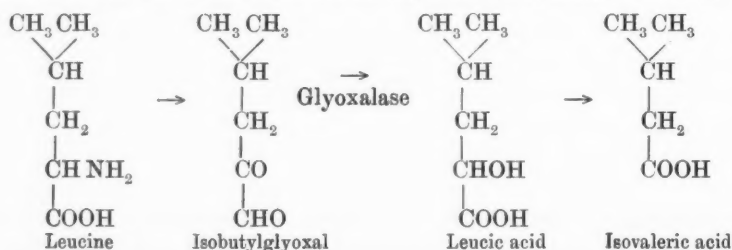
The *a*-hydroxy acids would then be converted into acids containing one carbon atom less, which would then be oxidized in the ordinary way : that is, those acids which are capable of producing acetoacetic acid would produce that substance. The amino-acids which are known to produce acetoacetic acid on perfusion through the liver are leucine, histidine, phenylalanine, and tyrosine.

Embden and Engel (92) showed that in such experiments synthetic leucine gave a good yield of acetoacetic acid, and Embden (93) showed that it was the dextro- or unnatural leucine which caused its formation, but that the laevo- or natural leucine if used in excess would also produce acetoacetic acid. Dakin (94) showed that histidine gave acetoacetic acid but only by an indirect series of reactions. Embden, Salomon, Schmidt (95) showed that phenylalanine and tyrosine were good acetoacetic acid producers. Now if leucine yields acetoacetic acid, then according to the above scheme isovaleric acid should do so, and this is the case (95). But if phenylalanine is broken down in accordance with the above scheme phenylacetic acid would be formed and excreted as phenaceturic acid. Dakin (96) supposes therefore that the benzine ring is opened before this stage is reached and that acetoacetic acid is produced thus:

$$
\begin{array}{llll}
COOH & COOH & CO_2 + H_2O & \\
| & | & \overline{} & \\
CHNH_2 & CO & COOH & COOH \\
| & | & | & | \\
CH_2 & CH_2 & CH_2 & CH_2 \\
| & | & | & | \\
C & 1\;C= & 1\;C= & 1\;CO \\
& | & | & | \\
& 2\;CH & 2\;CH & 2\;CH_3 \\
& \| & \| & \\
& 3\;CH & 3\;CH & \\
& | & | & \\
& 4\;CH & 4\;CH & \\
& \| & \| & \\
& 5\;CH & 5\;CH & \\
& | & | & \\
& 6\;CH= & 6\;CH= &
\end{array}
$$

(benzine ring structure for (1) with positions 1–6: HC 2, 6 CH; HC 3, 5 CH; 4; CH)

(1)   (2)   (3)
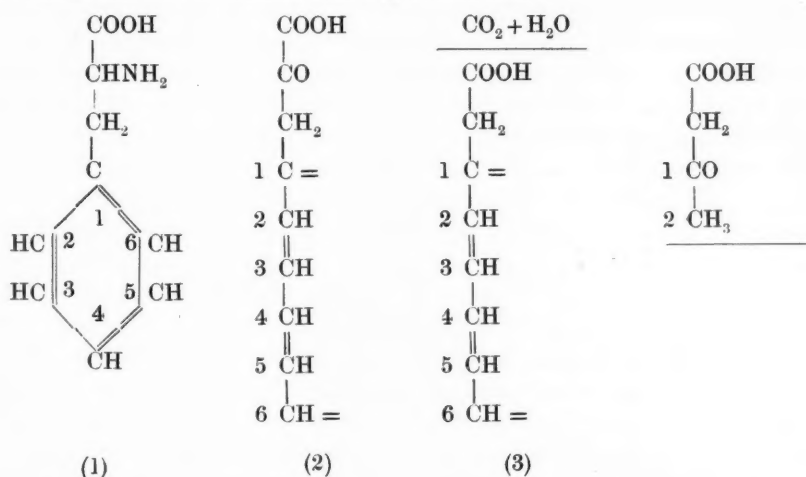
It is worth remarking that the opened chain of six atoms is just such as would be likely to form one of Collie's (loc. cit.) multiple ketene compounds: thus compound (3) might become $COOH\,CH_2\,CO\,CH = COH\,CH = COH\,CHO$ by addition of $3\,O = COOH\,CH_2\,CO\,CH_2\,CO\,CH_2\,CO\,CHO$ the tautomeric form. From this acetonedicarboxylic acid could easily be formed which on losing CO_2 would yield acetoacetic acid.

Leucine, phenylalanine and tyrosine have been given to diabetic patients and shown to produce acetoacetic acid. Baer and Blum (97) gave 33·75 grm. of leucine to a severe diabetic and obtained an increase of 6·3 grm. of total acetone bodies expressed as oxybutyric acid. The same authors also gave (98) to a girl of 15 years who was a severe diabetic 33 grm. of phenylalanine and 36·2 grm. of tyrosine and obtained considerable increases of acetone bodies after each.

It must be remarked that the leucine caused a considerable increase in the volume of the urine (2,160 to 2,600 c.c.) and I should attribute some of the increase of the acids to this circumstance; also the leucine given contained 3·6 grm. of nitrogen, none of which was excreted (11·5 grm. N. day before;

11·5 grm. N. on leucine day ; 12·0 and 9·1 on each of next two days). I should explain this retention of nitrogen, at all events in part, in the way already indicated. In the case of the phenylalanine and tyrosine there were not only remarkable increases of the acids but also of sugar :

Day of Exp.	Sugar.	Total acetone bodies as oxybutyric acid.	
23	32·3	24·2	
24	28·8	15·8	
25	42·0	28·2	Phenylalanine
26	40·0	18·9	
27	40·0	21·9	
30	32·3	23·7	
31	49·5	32·7	Tyrosine
32	45·5	25·2	

Here also I should be inclined to attribute a part of the observed increase of oxybutyric acid to increased diuresis as shown by the increased sugar.

Leucine also produces an increase of acids when given to a normal man : thus Borchardt and Lange (99) found an increase after the former had taken 28 and 30 grm. on successive days, the total acids as oxybutyric being 1·26 on the day before the leucine was taken, then 1·78 (some lost), 2·28, and 1·80 grm. : nitrogen was retained in this experiment in the same remarkable way as in Baer and Blum's case—for the same four days as above it was 17·98, 16·86 (some loss), 17·14, 17·30 grm. respectively.

Even if we admit that the observed increases in these instances of feeding with leucine, &c. are due entirely to the amino-acid and not to any secondary effect, they are insufficient to account for more than small amounts of the four carbon atom acids. An approximate idea of the amount of acetoacetic acid which could be formed in this way may be obtained as follows. Caseinogen of milk contains 11·7 per cent. of leucine, 3·2 per cent. of phenylalanine, and 4·5 per cent. of tyrosine. Reckoning that each molecule of amino-acid could give one molecule of acetoacetic acid, 100 grm. of casein could produce 12·5 grm. of acetoacetic acid. The other protein of milk lactalbumin occurs in small amount but is nearly twice as rich in leucine and poorer in tyrosine. As regards these three amino-acids ox-muscle (meat) is not very different from caseinogen, being a little richer in leucine and poorer in tyrosine. We may suppose that all the proteins in the diet of P. B. on 22/iv/14 gave per grm. of nitrogen about the same amount of acetoacetic acid as the milk protein, that is, 0·78 grm. of acetoacetic acid per grm. of nitrogen. Then on a theoretical yield of acetoacetic acid from these three amino-acids we might obtain about 25 grm. of it from the 32 grm. of nitrogen in P. B.'s diet on this particular day. The yield, however, would, as we have seen, be far short of the theoretical ; if it were 10 per cent. the acid produced would only amount to 2·5 grm. In this way therefore only a small fraction of the acids produced (56·9 grm.) could be accounted for.

We saw in the case of P. B. that while he was losing nitrogen he excreted an increasing amount of the four carbon atom acids. Cathcart (100), following Landergren, has shown that a normal man on a fat diet only, loses nitrogen

more rapidly than on a carbohydrate diet.   Baer (101) showed that phloridzined dogs excreted the four carbon atoms when they lost nitrogen, the amount of acids increasing at constant loss of nitrogen, but that on nitrogen equilibrium the acid-production ceased, and further the acid production was not influenced by wide variations in the amount of fat given.   In the case of W. H. R. on a rich protein fat diet the amount of acid kept relatively low.   Baer (loc. cit.) expressed the view that certain protein groups are concerned in the production of the acetone bodies, not so much in the sense that these groups are the material from which the acids are formed, but rather in the sense that they are the tools by which the acids formed.   In order to explain the results just referred to it appears to the writer to be unnecessary to make such an assumption as that of Baer.   In all these cases the man or animal as the case may be is able to catabolize much smaller amounts of carbohydrate than the normal individual ; he has therefore to depend almost exclusively on his ability to catabolize fat and protein for the energy he requires and for the repair of waste.   If much fat and little protein are given to him he will catabolize more fat : if the ratio of protein to fat in his diet be increased he will now catabolize more protein and less fat.   Making the very probable assumption that per gramme catabolized fat produces more acetoacetic acid than protein, we have a satisfactory explanation of the observed facts.   Baer's observation of increased acetoacetic acid production at constant loss of nitrogen is probably a transitory phenomenon observed during the time the body takes to establish a new equilibrium between fat and protein catabolism.   On nitrogen equilibrium the dog being a carnivorous animal does not require carbohydrate, so on fat and sufficient protein alone he produces no acetoacetic acid.   (See pp. 400–1.)

The Origin from Carbohydrate.

We have seen that Hugounenq first indicated the possibility of oxybutyric acid production from sugar by way of aldehyde and aldol.   But as it had been shown that both the normal and diabetic animal reacted to a withdrawal of carbohydrate from the diet by the production of ' acetone ', and that the restoration of this article of diet abolished the ' acetone ' in the one case and reduced its amount in the other, the view that acetoacetic acid could be produced was abandoned.   Only recently has the possibility of its production from this source been reconsidered.   Embden and Oppenheimer (102) regard pyruvic acid as a principal intermediate product in the catabolism of lactic acid, and this acid as is known is easily formed from carbohydrate.   Now they show that pyruvic acid on perfusion through the liver is a strong acetoacetic acid producer.   They also regard acetaldehyde as a normal intermediate product of the breakdown of carbohydrate.   But Friedmann (103) showed that aldehyde-ammonia was a strong acetoacetic acid producer.   Aldehyde also in contact with alkaline salts especially on warming easily condenses to aldol, and this substance when perfused

through a liver is a powerful acetoacetic acid former (103). I may add that
I have observed that aldol when oxidized by hydrogen peroxide in presence
of a trace of ferrous sulphate immediately gives a powerful reaction for aceto-
acetic acid. Embden and Oppenheimer regard this acetoacetic acid formation
from sugar only as a subsidiary reaction. But even so we see that sugar is
a probable source of a part of the four carbon atom acids. These substances
therefore must be regarded as arising chiefly from fat, to a less extent from
protein, and to a still smaller extent from carbohydrate.

The Relationship between Acetoacetic Acid, β-Hydroxybutyric Acid, and Acetone in Diabetes.

The acetone in diabetic urine is undoubtedly derived from acetoacetic acid
and, as we have seen, forms only a small fraction of it. The acetone in the breath
of the diabetic is without doubt also derived from the decomposition of the
alkaline salts of acetoacetic acid which circulate in the blood—if, as was pointed
out, these salts decompose slowly when urine containing them is allowed to stand
in a warm room, something similar is likely to occur in the blood. The extent
to which this occurs is probably not constant—determinations by the same
author do not give the same result. Schwarz (53), expressing all three substances
as oxybutyric acid, found that in a severe diabetic the breath acetone amounted
to 15·3 per cent. of the total on an average of eight days, the minimum being
7·9 and the maximum 23·5, while the oxybutyric acid average was 41·2, the
minimum being 25·9 and the maximum 56; but the minimum oxybutyric acid
occurred on a day when the breath acetone was 22·8 per cent. of the total and
the maximum oxybutyric acid on a day when the breath acetone was only
9·4 per cent. of the total. Schwarz remarks that in some cases the percentage
of oxybutyric acid is higher than in this case, namely 60 to 70 per cent., and
that its percentage increases with the severity of the case. In my cases I have
not determined the breath acetone, but as they are all severe cases it is certain
that the percentage would be a low one.

As regards the other two substances the question arises—which of these
is the primary product ? Blum (104) is definitely of the opinion that acetoacetic
acid is the primary product. He gave to a dog subcutaneously 3 to 4 grm.
per kilo body weight of sodium acetoacetate and observed that it excreted both
acetoacetic acid and *l*-oxybutyric acid; but on giving in the same way 8 grm. per
kilo of oxybutyric acid, unchanged acid appeared in the urine and there was no
increase in the acetoacetic acid. Sodium acetoacetate was also given to normal
and to slightly diabetic men and oxybutyric acid was found in the urine. Blum
concludes that acetoacetic acid is difficult to burn, that it is converted in the
body into oxybutyric acid, and that if the latter is oxidized by way of aceto-
acetic acid in the body its administration must lead to an excretion of
acetoacetic acid, which does not happen. Others, however, have obtained
different results. Minkowski (105) gave sodium *l*-oxybutyrate (10 grm.) to

a dog on the fifth day after removal of the pancreas and found that the urine, which gave no reaction before, now gave a strong reaction for acetoacetic acid. Zeehuisen (106), after two days carbohydrate starvation, took 12·5 grm. of sodium oxybutyrate and after it excreted much acetone and acetoacetic acid but no oxybutyric acid.   Waldvogel (107) gave 5 grm. of sodium oxybutyrate to two normal men, to one slight and to one severe diabetic and observed a doubtful increase of the breath acetone in one normal case and an undoubted increase of acetoacetic acid in the diabetic cases.   McKenzie (108) gave the sodium and potassium salts of the inactive acid subcutaneously to dogs and observed the presence in the urine of acetone and acetoacetic acid, and some laevo-rotatory oxybutyric acid, showing that the dextro-acid was more readily attacked than the laevo-acid.   Dakin (109) gave 10 grm. of inactive oxybutyric acid as sodium salt by mouth to a 1·7 kilo rabbit, 3 grm. as sodium salt intra- venously to the same, and 8 grm. as sodium salt to a 6 kilo dog subcutaneously, and observed in the first two cases a small increase in the acetoacetic acid excreted and in the last case that a small amount of the laevo-rotatory acid was excreted.   Marriott (110) gave the inactive sodium salt subcutaneously to a sucking-pig, and the same salt of both the inactive acid and the laevo-rotatory acid in the same way to phloridzined dogs, and found that the pig gave a small amount of acetoacetic acid, equal to 0·1 of the oxybutyric acid, while the dogs gave practically no increase of acetoacetic acid, readily burned the dextro-acid, and excreted from 65 to 90 per cent. of the laevo-acid unchanged. Dakin (70) gave phenyloxypropionic acid as sodium salt subcutaneously to each of three dogs ; most of it was oxidized to benzoic acid, a small part was excreted as the laevo-acid, but in each case a little benzoylacetic acid was formed.

From all these results it is clear that the living organism can convert oxybutyric acid into acetoacetic acid, but only to a very limited extent.   As regards the results with freshly isolated tissues, they are similar to the above. In their perfusion experiments Embden, Salomon, and Schmidt (95) found that l-oxybutyric acid was a powerful acetoacetic acid producer, but the blood must be kept aerated to the utmost to obtain the result.   Wakeman and Dakin (111) showed that dog's liver contains an enzyme, they call it β-oxybutyrase, which converts the salts of oxybutyric acid into salts of acetoacetic acid in the presence of abundance of air or oxygen, whose activity is increased by the presence of blood, or of oxyhaemoglobin, or of blood serum.   These authors noticed that liver pulp containing this enzyme failed to effect the change in the absence of air or oxygen.   Marriott (loc. cit.) made similar experiments with blood, fresh liver pulp, and muscle, and with similar results.   The inference from these experiments with tissues is that already drawn—under the normal conditions oxybutyric acid is very difficult to oxidize to acetoacetic acid.

On the contrary, acetoacetic acid is reduced to oxybutyric acid with great ease and indeed asymmetrically, that is, with production of the laevo-acid. Pollak (112) showed that sodium acetoacetic, when digested in an incubator with 0·6 per cent. salt solution and the filtrate, through cloth, of minced ox liver

ground with sand, was decomposed to the extent of 50 per cent. in twenty-four
hours.   He tried many other substances and found that they too decomposed the
salt under the same conditions—kidney infusion decomposed 82 per cent., blood
serum of the horse 62 per cent., alanine 90 per cent., tyrosine 24 per cent.   But
Pollak thought that the only products of decomposition were acetone and carbon
dioxide.   Other authors, however, showed that the tissues of animals when
digested with salts of acetoacetic acid caused the acid to disappear to a
considerable extent without the production of acetone.   Embden and Michaud (113)
showed that liver pulp, if quite fresh, could decompose from 50 to 60 per cent.
of small amounts of sodium acetoacetate, and smaller percentages but absolutely
larger amounts of larger quantities of the salt; blood, kidney pulp of the ox, and
muscle pulp of dogs were all active, but less so than liver.   They thought that
the product must be acetic acid, but were unable to demonstrate its presence.
Friedmann and Maase (114) added sodium acetoacetate to defibrinated ox-blood,
and perfused it through a dog's liver, and obtained 40 to 60 per cent. of the
acetoacetic acid in the form of oxybutyric acid, and the acid was laevo-rotatory:
they also observed the reduction of acetoacetic acid to oxybutyric by liver pulp.
The enzyme which effects this reduction they call Ketoreductase.   Wakeman and
Dakin (115) had observed the disappearance of sodium acetoacetate on digestion
with liver pulp and thought it might be due to the formation of acetic acid; but
Dakin (109) had at the same time as Blum (104) shown that when sodium aceto-
acetate is injected intravenously into cats and dogs laevo-rotatory oxybutyric
acid was found in the urine—from 12 grm. of the former, between 1 and 2 of the
latter.   Now Wakeman and Dakin repeat their experiments with liver pulp and
isolate l-oxybutyric acid—they obtain a yield of about 22 per cent. in seven hours
at 40°.   Friedmann (116) and also Dakin (117) re-examined the effect of giving
benzoylacetic acid to animals, an experiment first made by Knoop (67): the
results of the two former confirmed Knoop, in so far as he stated that much
of the substance was oxidized to benzoic acid, but extended his results by
showing that some phenyl-β-oxypropionic acid was formed which was laevo-
rotatory, also a little acetophenone, some cinnamic acid, while a little unchanged
acid was always excreted.   Then Lagermark (118), examining other tissues than
liver pulp, found that sodium acetoacetate was reduced to l-oxybutyric acid by
muscle and kidney pulp but not by blood, lung, pancreas, and spleen.   Finally,
Marriott (loc. cit.) gave sodium acetoacetate subcutaneously to a sucking-pig and
obtained an increased excretion of acetoacetic acid, but a much greater increase
in the excretion of oxybutyric acid; he gave the same salt in the same way
to phloridzined dogs and in two cases found the proportion between the
oxybutyric and acetoacetic acids excreted to be 2 to 1, while in the third animal
it was 1 to 1.   He believes that a small part of the oxybutyric acid excreted was
dextro-rotatory.

From all these results it must be concluded that the reduction of acetoacetic
acid to oxybutyric acid is accomplished by the body under ordinary conditions
far more readily than the oxidation of oxybutyric acid to acetoacetic acid; the

latter change can be accomplished, but only under abnormal conditions as regards the presence of oxygen.   Moreover, it is clear that this evidence renders strong support to the hypothesis of Blum, a hypothesis which is supported by Dakin and by Marriott, that of these four carbon atom acids acetoacetic acid is the primary product.   Another point also emerges very clearly, namely, that of the three substances, acetoacetic acid, l-oxybutyric acid, d-oxybutyric acid, the first two are very difficult to catabolize by the animal body, while the third is pretty easily catabolized.   Dakin has drawn attention to the fact that when phenylpropionic acid is given to dogs there is no unchanged acid to be found ; also when cinnamic acid is given to dogs there is no unchanged acid to be found ; and that from both these substances the same intermediate products (those given on p. 372) are obtained.   When phenyl-β-oxypropionic and benzoylacetic acids are given there is always unchanged acid.   This important observation shows that both the saturated and unsaturated acids are more easily attacked than either the hydroxy or the ketonic acid formed from them.   Now crotonic acid is a powerful acetoacetic acid producer when perfused through the liver— Friedmann (119) ; and a powerful oxybutyric acid producer when incubated with liver pulp in presence of oxygen—Friedmann and Maase (120) ; and when it is given subcutaneously to a dog in the proportion of 1 grm. per kilo it gave oxybutyric acid and no acetoacetic acid, but at 2 to 3 grm. per kilo it gave acetoacetic acid—Blum (104).   This author showed also that the effect of crotonic acid was independent of the store of glycogen in the dog's body and that this acid is far more toxic than oxybutyric acid.   In this connexion it may be noticed that Albertoni gave 1 to 2 grm. of the acid to rabbits without observing any effect but that the aldehyde of this acid was excessively toxic, 1 c.c. causing the death of a 4·5 kilo dog in ten minutes, and that the symptoms of poisoning caused by seven drops in a rabbit of 1·2 kilos were those of diabetic coma. At first sight it appears difficult to account for the production of acetoacetic acid by the direct oxidation of crotonic acid without the intermediate formation of oxybutyric acid ; but the scheme suggested on p. 373 would apply : acetoacetic acid would be the first product, and this would be reduced in the usual way. The question of the toxicity of the acid, if it were formed as an intermediate product in the oxidation of butyric acid, as, for example, in Joslin's experiment, would not arise, for very little free acid would occur on this scheme.

The Place of Formation of Acetoacetic Acid.

Embden and his fellow workers are strongly of opinion that the only place of formation of acetoacetic acid is the liver.   They base this conclusion on the fact that acetoacetic acid is produced, when blood, to which suitable substances have been added, is perfused through the surviving liver, and on the fact that this acid was not found by them in similar experiments on other organs (121). Thus Embden and Wirth (122) resent Abderhalden's statement in his *Lehrbuch der physiologischen Chemie* (1909, p. 142) that the place of formation of the

acetone bodies is unknown. In the last edition of that book (1914, p. 200), Abderhalden modifies his former statement so far as to say that we know one organ in which the substances may be formed if we do not know any others. My own opinion is that only small quantities of acetoacetic acid are formed in the liver in the animal organism, and that the liver is rather the chief place of its reduction to oxybutyric acid; and I proceed to substantiate this opinion as follows:

The success of the perfusion experiments with the freshly excised or surviving liver made by Embden and his followers is dependent on such a supply of oxygen to the perfused blood as is not normally to be found in the liver. Embden and Lattes (123) perfused the livers of a dog which had fasted eight days, of dogs which had been given phloridzin, of dogs from which the pancreas had been removed, with blood only. Since dogs, unlike men, do not excrete the four carbon atom acids on fasting, the starved dog, as was to be expected, gave only a small increase of acetoacetic acid; but in all the other cases large increases were obtained, comparable in some cases with those obtained from butyric acid itself, but still less than those obtained when 3 to 3·5 grm. of oxybutyric acid itself was added to the perfusion blood and the liver of a normal dog was used. These results are so important for my view that I give a few of them taken from various papers:

	Total 'acetone' mg.
Phloridzined dogs. No addition to the blood . .	108 : 169 : 210
Depancreatized dogs. ,, ,, ,, ,, . .	114 : 196 : 223
Normal dogs. 2 grm. butyric acid added to blood .	173 : 237
,, ,, 3 to 3·5 grm. oxybutyric added to blood	197 : 206 : 419 : 430
,, ,, 2·5 to 3·0 grm. tyrosine added to blood	133 : 198
,, ,, 2·0 grm. leucine added to blood . .	119 : 148 : 150

Embden and Lattes took the precaution of showing that control lobes from the liver of each dog in their experiments gave no more than a trace of volatile iodoform-yielding substances, so that the acetoacetic acid they obtained must have been formed by the perfusion process.

Now the explanation I offer of these experiments is this: that they show clearly that in the surviving liver there is no acetoacetic acid, or not more than a trace just in cases where it would be expected to be present in more than traces if Embden's view were correct; that their acetoacetic acid was derived chiefly from oxybutyric acid, which would inevitably be present on my view, and perhaps to a small extent from traces of those amino-acids which yield aceto-acetic acid. Embden and Lattes say that they convinced themselves that oxybutyric acid is only present at most in traces in the diabetic liver—but they do not furnish further data on this point. The reply to this assertion is that as their livers were about 250 grm. in weight, only traces on any known method of determining oxybutyric acid would be found unless the liver contained really very large amounts of the substance. We have also to remember that the whole of what Embden reckons as acetone is in all probability not acetone only but acetone and other iodoform-producing substance or substances.

Geelmuyden (124) determined the acetoacetic (expressed as acetone) in the organs of patients who had died in coma and in one normal person: these analyses were made in from twelve to twenty-four hours after death. He also determined (125) both acetoacetic acid (as acetone) and oxybutyric acid in the organs of coma patients. Analyses were made after the organs had stood for some days after death; e.g. in two different cases:

M. M. 100 grm. liver gave 12·5 and 5·1 mg. acetone on 28/xi and 30/xi.
A. A. „   „   „   „   9·5 and 7·8 „   „   „   6/xi and 12/xi.
A. Z. „   „   muscle   „   26·1 and 13·9 „   „   „
         „   „   „   „   34·8 and 27·0 „   „   „   4/i and 15/i.

It is seen that there is a decrease in the amount of acetoacetic on keeping the organ, but this decrease is not more marked in the liver than in other organs. Now I give a table of Geelmuyden's results, taking the earliest analysis in every case:

Acetone in mg. obtained from 100 grm. of the organs of patients who died in Diabetic Coma. One normal case is given. Compiled from Geelmuyden.

Sex	♂	♀	♀	♀	♂	♀	♂	♂	♂	♂	♀ *
Age	14	20	48	48	30	42	32	31	47	28	31
Liver	9·6	6·9	11·4	9·6	9·5	6·3	12·5	2·2	14·5	26·2	0·7
Brain	—	—	55·1	50·7	35·6	—	19·5	19·5	51·4	—	2·9
Kidney	19·1	28·8	65·4	44·9	41·0	23·4	16·6	11·4	41·8	47·8	2·9
Muscle	18·2	—	30·3	27·4	26·1	18·0	18·9	19·0	34·8	53·8	3·7
Lung	—	28·8	35·8	47·0	27·7	34·4	16·2	12·3	50·3	—	—
Blood	—	—	67·4	54·3	—	—	—	16·1	50·6	53·2	4·3

* Not diabetic.

Geelmuyden showed that the decrease of the acetoacetic acid in the liver was accompanied by an increase of oxybutyric acid. This author supports the view of Waldvogel (loc. cit., p. 67) that the place of formation of the acetone bodies is not to be sought in one specific organ. These figures of Geelmuyden strongly support such a view, and it is the writer's opinion that they show quite clearly that the liver is not the place of acetoacetic acid formation, but rather, as will appear later, the chief place for its reduction to oxybutyric acid.

The distribution of acetoacetic acid and oxybutyric acid in the tissues of phloridzined dogs has been determined by Marriott, who found the liver contained most oxybutyric acid, the blood contained most acetoacetic acid (7·6), while the liver and muscle contained 2·8 and 1·3 respectively; the figures are milligrams per 100 grm., and I question the significance of such minute figures as those for the liver and muscle. Sassa (127) determined the oxybutyric acid in the organs of phloridzined dogs, and in two cases where there was considerable 'acidosis' there was more of this acid in the liver than in the blood, muscle, or lungs, but in one case less than in the kidney—in the other case the kidney was not analysed: he also determined the oxybutyric acid in the organs of three

patients who died in diabetic coma and found in all three more oxybutyric acid in the liver than in any other organ : he obtained traces of the acid in the organs of a normal man, and again the oxybutyric acid was highest in the liver.

If an explanation of the production of acetoacetic acid from such a substance say as butyric acid by the perfused liver be required, it could be found by assuming that the surviving liver produces a reducing substance which, in presence of a free supply of oxygen, acts as a carrier of this element after the fashion of benzaldehyde. Such a supposition would fully account for the requirements (a), (b), and (c) on p. 368. The writer has found that reduced iron dissolved in a solution of butyric acid—ferrous butyrate—oxidizes on exposure to air or oxygen simply, at a surprising speed, and the liquid yields acetone on distillation. Again, if a solution of ammonia butyrate, to which a little phosphoric acid and ferrous sulphate have been added, be submitted to a current of air at 48°, 4 per cent. of the theoretical yield of acetone can be obtained in seventy minutes.

The Action of the Four Carbon Atom Acids and Acetone in Diabetes.

One after another these three substances have been held to be responsible for the phenomenon of diabetic coma. They have all been examined again and again as to their toxicity, and on the results of these examinations they have been held by some to be toxic and by others to be non-toxic.

Kussmaul, working under Frerichs, had tested the action of acetone on men and animals, but was unable to produce the symptoms of diabetic coma. Frerichs (26) (Appendix II to his paper) had the question reinvestigated by Brieger, and the latter gives the result of numerous experiments by Salomon. Healthy men and diabetics, whose urine had given the ferric chloride reaction for a long time, took 20 grm. of acetone on five successive days without suffering any symptoms whatever. Albertoni (128) concluded that for dogs the fatal dose was 8 grm. per kilo. Penzoldt (129), however, does not accept Frerichs's results as conclusive : he suggests that the conditions for its action may be like those for curare, which does not exert its toxic action when given by the stomach but does so when the kidneys are ligatured. To test this he gives 1·0 c.c. of acetone subcutaneously to a 0·65 kilo rabbit and places it under a bell-jar to restrict the excretion of acetone. It was dyspnoeic in ten minutes, while a control rabbit of the same litter showed no symptoms. From this and other experiments he concludes that while the toxic action is not strong it is present, and that acetone intoxication may co-operate in the comatose state.

Tappeiner (130) made very careful experiments on dogs and rabbits, measuring the blood-pressure, the pulse and respiration frequency, and the temperature ; and he gave the acetone by inhalation. More than half of it was exhaled. First it produced a rise in all the above measurements, then depres-

sion, complete anaesthesis, relaxation of muscles, cessation of reflex activity, then a fall in all measurements till death, which results from paralysis of respiration. To cause death, as the action is a gradual one, large quantities of acetone are required and the inhalation must be prolonged. Schwarz (131) ligatured the neck of the bladder of a dog and gave it a gram of acetone; the animal died in twenty hours.

Acetoacetic acid was examined as to its toxicity by Frerichs-Brieger (loc. cit.). Doses of 10 grm. given as free acid or as sodium salt to man and dogs vanished completely. Doses up to 40 grm. were given ; these did cause the excretion of acetone, but no dose ever caused the urine to give the ferric chloride reaction. There was no increase of breathing frequency, no somnolence, and so on; but the breath had a peculiar aromatic smell. When 25 grm. of the acid or its sodium salt were given subcutaneously to dogs, or even when injected into the blood-stream, there were no symptoms; acetone was present in the urine, but the latter never gave the ferric chloride reaction. Albertoni (loc. cit.) also examined the action of acetoacetic acid ; his results agree with those of Frerichs, except that he observed albuminuria in dogs after 10 grm. of the acid had been given. When, however, bicarbonate of soda was given before and after the acid the urine was found to contain acetoacetic acid.

Schwarz (131) gave sodium acetoacetate to a dog in the proportion of 2 to 3 grm. per kilo and found no acetone in the breath and no ferric chloride and no iodoform reactions in the urine. A dog of 4·1 kilos, which had taken 10 grm. of the sodium salt, was depancreatized and four days afterwards the same dose of the salt was given. The urine which, before the experiment, gave no ferric chloride now gave a strong reaction, and the breath which had only contained a little acetone now contained a great deal. The dog died after the experiment, and Schwarz attributes its death to duodenal necrosis. Another dog was given 6 grm. of the salt on the second day after removal of pancreas. There was no ferric chloride reaction, but the dog excreted by breath and urine much acetone. Schwarz concludes that the 'oxidation' of acetoacetic acid in the diabetic organism takes a different course from that which it takes in the normal organism. Geelmuyden (132) took 20 grm. of sodium acetoacetate himself, first on a normal diet, then on a carbohydrate free diet; he found that on the former diet only 0·73 per cent. of the acetoacetic acid was excreted, while on the latter diet 6·20 per cent. was excreted. This author concludes that restriction of carbohydrate in man impairs his power of transforming acetoacetic acid. Porges (133) relates that he and Salomon gave acetoacetic acid to depancreatized dogs and observed in one case a great increase in the sugar excretion; in another a rise of the D : N quotient; but owing to the high degree of toxicity of acetoacetic acid in these animals these were the only two out of fifteen which could be kept alive for several hours after the administration of the acid. Neubauer (43) gave 30 grm. of acetoacetic acid as sodium salt to severe diabetics and found that it caused 'a considerable increase' in the excretion of both the four carbon atom acids. Further details of these experiments are not available; but it is clear

from them that the severe diabetic is unable to deal with more than a limited amount of acetoacetic acid.

Dakin (109) gave 10 grm. of acetoacetic acid intravenously as the sodium salt to a puppy of 3 kilos weight; it died in four hours. A large dog was given 12 grm. of the acid in the same way and made a perfect recovery: the urine contained 1·51 grm. of l-oxybutyric acid.

From these results we may infer that in normal adults acetoacetic acid is scarcely, if at all, toxic; in young animals it is rather toxic; in depancreatized animals which come near to the true diabetic it appears to be highly toxic. Many experiments have been made on the toxicity of oxybutyric acid; they all agree in showing that it is practically non-toxic. Blum (104) estimates the fatal dose at 8 to 10 grm. per kilo body weight in the case of dogs.

The Cause of Diabetic Coma.

Chiefly owing to the work of Magnus-Levy, oxybutyric acid has been held by many to be the cause of coma; its mode of action, as we have already seen, has been believed to be simply that of an acid. It cannot, however, act by rendering the blood and tissues actually acid, and this difficulty was recognized by Magnus-Levy. In fact the reaction of the blood of diabetic patients is not different from that of normal men until coma actually occurs, when there is perhaps always a slight rise. The only proper measure of the reaction of blood is the hydrogen ion concentration, and this constant has been determined for blood by a number of observers: Hober, Szili, Benedict, Rolly, Masel (134). (See paper by last named for literature.) I give some of Masel's results: each result is the mean of two determinations. See also some results of Poulton referred to below:

Case.	Hydrogen ion Concentration.
Normal man. Fasting. Gr	$3·06 \times 10^{-8}$
„ „ „ Si	$3·24 \times 10^{-8}$
Precomatose diabetic. K	$3·06 \times 10^{-8}$
„ „ G	$3·09 \times 10^{-8}$
„ „ P	$2·62 \times 10^{-8}$
„ „ H	$3·02 \times 10^{-8}$
„ „ S	$3·36 \times 10^{-8}$
Diabetic coma : immediately before death . .	$7·65 \times 10^{-8}$
Dog—12 days after removal of pancreas ; blood taken during deep narcosis *	$9·70 \times 10^{-8}$
Normal dog. Fasting	$2·66 \times 10^{-8}$
Dog : deep narcosis *	$5·30 \times 10^{-8}$

* By morphine; atropin; ether.

Here then there is no difference in reaction between the blood of a normal man and of a precomatose diabetic; but in actual coma immediately before death there is a small increase of acidity. In all these precomatose cases the acetoacetic acid reaction was very strong. If the blood in the precomatose state is neutral, then the acids may be supposed to act by withdrawing alkali from the

body as the mineral acids do, and this explanation was advanced by Kraus and Honigmann (28) and greatly emphasized after them by Magnus-Levy. Now Magnus-Levy bases the alkali withdrawing power of oxybutyric on the thesis that the free acid does not pass into the urine. If this can be shown to be the case, Magnus-Levy's conclusions are clearly left in the air. Henderson (135) has shown that the phosphates play the fundamental part in regulating the excretion of bases from the body by way of the urine. When bases are required by the body for the neutralization of acid they are conserved by the phosphates being excreted as the acid phosphate : thus suppose that all the phosphate is excreted in an alkaline urine as M_2HPO_4, while in a very acid urine they are all excreted as $M H_2PO_4$, then by this change one atom of a monovalent base (M) has been kept in the blood for the neutralization of acid. This conservation of base by phosphoric acid is ignored by Magnus-Levy. Henderson (loc. cit.) further shows that in a very acid diabetic urine there must necessarily be much free oxybutyric

acid. He establishes the formula $(\overset{+}{H}) = \frac{HA}{MA} \times C$ where $(\overset{+}{H})$ is the hydrogen ion

concentration in a solution; the fraction $\frac{HA}{MA}$ is the ratio of the free acid to

neutral salt of the same acid in a given volume of the solution; and C is the dissociation constant of the acid divided by the degree of ionization of the salt. The formula only holds for weak acids such are included in the table below, and in this case the degree of ionization of the salt is so nearly unity that C may be taken as the dissociation constant of the acid. If X be the percentage of free

acid in the solution the formula may be recast thus: $X = \frac{100\,(\overset{+}{H})}{C + (\overset{+}{H})}$. From this

formula Henderson constructs curves showing the percentages of the commoner urinary organic acids which must be present in the free state in the blood and in urines of various acidity. I venture to construct from Henderson's formula the following table which should be of use in studying the free acids in the urine; under C are given the dissociation constants of the free acids—these are the proper measure of the strength of the several acids; the figures in the columns opposite each acid give the percentage of the total acid which must be free in the fluid named at the head of the column. For example, blood has a hydrogen ion concentration of $3 \cdot 0 \times 10^{-8}$, and in such a fluid, if acetoacetic acid is present at all, only 0·02 per cent. of it can be in the free state.

Acid.	C.	Very acid urine. $(\overset{+}{H}) = 3 \times 10^{-5}$.	Acid urine. $(\overset{+}{H}) = 1 \times 10^{-5}$.	Normal urine. $(\overset{+}{H}) = 3 \times 10^{-6}$.	Blood. $(\overset{+}{H}) = 3 \times 10^{-8}$.
Hippuric	$2{,}200 \times 10^{-7}$	12·00	4·35	1·35	0·01
Acetoacetic	$1{,}500 \times 10^{-7}$	16·66	6·25	1·96	0·02
Lactic	$1{,}300 \times 10^{-7}$	18·75	7·14	2·25	0·02
Oxybutyric	200×10^{-7}	60·00	33·33	13·04	0·15
Uric	15×10^{-7}	95·24	86·96	66·66	1·96
Carbonic	3×10^{-7}	99·01	97·09	90·91	9·09
NaH_2PO_4	2×10^{-7}	99·33	98·04	93·75	13·04

This table shows, in quite an impressive manner, the function of the kidney in conserving base for the body and is in marked contrast with Magnus-Levy's assumption that oxybutyric acid is not excreted as the free acid. Moreover, it throws some light on Magnus-Levy's determinations in his important Case VI quoted on p. 312. On 7/vii/98 this boy excreted 157·1 grm. of acetoacetic acid and oxybutyric acid as determined by the excess of bases. Of this amount 23·6 grm. were acetoacetic acid, and therefore 133·5 grm. were oxybutyric acid. Magnus-Levy emphasizes the fact that the urine still remained acid. Assuming the acidity to have been that of an ordinarily acid urine, 33·3 per cent. of the oxybutyric and 6·25 per cent. of the acetoacetic acid must have been free, and therefore not included in the acid determined by the base excess method. Thus the real figures would be acetoacetic acid 25·2 grm. and oxybutyric acid 200·3 grm. On this same day the oxybutyric acid determined by extraction was only 101 grm. Which of these figures, if either, is correct I am unable to decide ; and so for all the figures in the table.

It is certain then that the amount of a weak acid, such as oxybutyric, required to produce an acid poisoning such as that caused by hydrochloric acid is enormously greater than Magnus-Levy's estimate, but it is equally certain that many people die of diabetic coma who do not produce any such quantities of acid. Another point apparent from the table is that acetoacetic acid is an acid 7·5 times as strong as oxybutyric acid, so that, although it occurs in smaller amount than the latter, yet in combining with base it is really far more effective than the latter. It is futile, then, even from the acid-poisoning point of view alone, to disparage the importance of acetoacetic acid as Magnus-Levy has done. These two acids must, of course, be provided with base as they are produced in the body ; all the strong bases are available for this purpose provided they are present in the patient's diet and, in addition, the body can provide ammonia if sufficient protein is given. The ammonia has already been considered (Case IV). Calcium, as is well known, plays an important part in neutralizing the acids ; this is well shown in my method of determining the oxybutyric acid. When there is a serious call upon this base there always appears a rich deposit of calcium sulphate in the extraction apparatus ; for instance, in Case IV such a deposit appeared on xii/1, 2, 3, 4, 5, and again on xii/16, 17, 18, 19, 21, 22, 23.

To show how nearly these two bases alone may suffice to neutralize the two acids, I give the following figures from a case, J. F., a man, aged 22 :

Date.	N (grm.).	NH$_3$ (grm.).	Acetoacetic acid (grm.).	Oxybutyric acid (grm.).	Ca (grm.).	Ca + NH$_3$ calc^d as Oxybutyric.
25/ii/15	24·9	3·71	12·3	21·2	2·19	34·1
26 ,, ,,	20·4	2·23	9·2	13·2	1·66	22·3
27 ,, ,,	27·0	2·53	13·4	24·6	1·86	25·2

It has to be remembered that ordinarily the diet of a diabetic is an 'acid' diet, so that his diet must provide sufficient base, not only to neutralize the acids

being produced, but also the sulphuric and phosphoric acids produced from the articles in his diet. For example, Shermann and Gettler (136) have shown that 100 grm. of egg and 100 grm. of lean meat produce acid requiring 11·1 and 13·9 c.c. of normal caustic soda (40 grm. per litre NaOH) for their neutralization. On the other hand, 1 litre of milk provides an excess of base requiring 18 c.c. of normal acid for its neutralization. The consequences of insufficient base in the diet of a normal man are serious, and they have been described by A. E. Taylor and are quoted by Robertson (137): diuresis is an early but not an abiding symptom, diaphoresis is always present, anorexia, a feeling in the [muscles similar to that experienced after hard and unaccustomed work, later slight and irregular twitchings in the peripheral muscles, expressed constipation, and, lastly, acetone in the breath and considerable amounts of acetone and aceto-acetic acid in the urine—in a diabetic they must be much more serious, and if we may judge from Taylor's experiment on himself they would actually provoke the formation of acetoacetic acid.

From the work of Henderson (loc. cit.) it is plain that phosphoric acid is no less important than the bases. On insufficient base a severe diabetic, no doubt through the effort to conserve base, suffers a serious loss of phosphoric acid. This is well shown by the experiments of Gerhardt and Schlessinger (138). They kept a severe diabetic on a constant diet and at first gave him bicarbonate of soda (four days), which was then withdrawn (nine days), and again restored (four days). The averages for these periods in two experiments were:

		Daily average P_2O_5 (grm.).	
		I.	II.
Fore-period	(NaHCO₃)	2·18	2·24
Middle period	(No NaHCO₃)	2·70	2·89
After-period	(NaHCO₃)	1·99	2·32

Taking the fore-period at 100 in each experiment, we have in Experiment I 123·8 and in Experiment II 129·0—that is, increases of 24 and 29 per cent. respectively.

It will be recalled that Case I derived great benefit from the administration of Harden and Young's hexosephosphoric acid, and I am inclined to attribute a part of this beneficent action to the phosphoric acid contained in this compound. J. H. B.'s diet was not poor in base, but undoubtedly the phosphoric acid would enable him to retain base and it is certain that he would not lose phosphoric acid.

I may notice that in Magnus-Levy's Case VI on the first day the loss of P_2O_5 was 3·75 grm.; then in succession 2·64, 1·30, 0·57, and 1·66. It seems as if his stock of phosphoric acid was depleted, so that he could not utilize properly the bases that he had—that is, the conserving effect of the phosphates would be absent.

In the attempt to counteract the supposed acid poisoning, enormous amounts of bicarbonate of soda have been employed with very poor success. One error in this treatment, as has been pointed out by Langdon Brown (139), is that the severe diabetic is not losing sodium alone, but all the strong bases as well,

namely potassium, calcium, magnesium, and ammonia, bases which are as essential for the life processes as sodium itself; but the effect of huge doses of bicarbonate of soda must be to replace these bases to a dangerous extent by sodium, a base unable to perform the same functions as the other bases. This probably accounts for the strange fall in potassium in Magnus-Levy's Case VI, which is as follows on successive days: 7·42, 7·32, 5·98, 4·0, 3·11. Both Beckmann and Hagentorn, working under Stadelmann (140), show that, in fact, sodium bicarbonate causes a loss of potassium and that the loss is proportionate to the amount given, unless the amount is small. In place of bicarbonate of soda alone, a mixture of several salts of weak acids, such as the one suggested by Langdon Brown (loc. cit.), is far preferable. Such a mixture, however, makes no provision for the loss of phosphoric acid. Another error in this treatment has been indicated by Kennaway (141), who draws attention to the powerful effects of the sodium ion on cardiac and striped muscle. The position as regards the so-called acid poisoning may be summed up as follows : (a) The blood in the precomatose stage has the same reaction as that of a normal person ; but in actual coma it may have a higher hydrogen ion concentration than normal, but even then not such as to be incompatible with life. (b) Phosphoric acid conserves the bases of the body ; and the fact that much oxybutyric acid can be excreted in the free state in the urine acts in the same way, so that the amount of the four carbon atom acids required to produce 'acid poisoning' is far greater than the amount claimed even by Magnus-Levy. (c) On the other hand the acids do require base, which if not supplied entails a serious loss of phosphoric acid. (d) A diabetic on a suitable diet can, with the aid of moderate amounts of an alkali, be supplied with sufficient base for all his requirements. (e) Yet in spite of (d) coma may occur. (f) The action of bicarbonate of soda in coma is nearly always, even in the hands of its most zealous advocates, a failure and utterly unlike its action in true acid poisoning, say, by hydrochloric acid. On these grounds I regard the acid poisoning theory of diabetic coma as not in accord with the known facts. I would suggest as an alternative theory that diabetic coma is due to poisoning by the salts of acetoacetic acid primarily, and to poisoning by acetone formed from these salts secondarily and in quite a subordinate degree. In support of this theory the following statement of facts may be made.

1. On the approach of coma there is an increase in the intensity of the ferric chloride reaction of the urine—that is, an increase in the excretion and therefore in the production of acetoacetic acid. This was observed in a striking series of cases by Frerichs as long ago as 1883.

2. If we consider the ratio of the acetoacetic acid to the oxybutyric acid (multiplied by 100 to give whole numbers) we find that with small amounts of the two acids the ratio is usually very high ; as the severity of the case increases the ratio tends to a value about 30 ; if the case threatens to end in fatal coma the ratio tends to rise again. In illustration of this I give the following table, in which the average value of the ratio is given for every rise of 5 grm. of

oxybutyric acid in the urine of severe diabetics—four of my own cases and one each of Kennaway (45), Loeb (55), and Joslin (66). The number in brackets indicates the number of observations on which the average is calculated; where there is only one observation for a step it cannot be regarded of course as the representative value for that step. The case J. F. is a peculiar one : he was a patient whose urine I analysed for several months altogether, first for a long period, then for a shorter period; he would not remain on a prescribed diet, and as the analyses showed, he took more carbohydrate than was assigned to him. The

$$\frac{\text{Acetoacetic acid}}{\text{Oxybutyric acid}} \times 100.$$

β-oxybutyric.	W. H. R.	P. B.	W. S.	J. F.	Kennaway's Case 4.	Loeb's case.	Joslin's case.
0 to 4·9	>100 (11)	—	—	—	—	96 (8)	—
5 to 9·9	64·5 (19)	—	35 (3)	79 (4)	—	53 (11)	—
10 to 14·9	51·0 (14)	33 (1)	36 (4)	63 (6)	32 (1)	33 (6)	....
15 to 19·9	39·6 (7)	32 (3)	33 (5)	60 (1)	37 (2)	—	—
20 to 24·9	36·0 (9)	31 (6)	36 (12)	54 (3)	35 (8)	—	—
25 to 29·9	33·4 (9)	28 (4)	36 (7)	53 (1)	37 (2)	—	—
30 to 34·9	—	28 (5)	33 (3)	—	35 (8)	—	—
35 to 39·9	—	29 (6)	—	—	—	—	—
40 to 44·9	—	29 (9)	—	—	—	—	—
45 to 49·9	—	28 (1)	—	—	—	—	—
55·9							54 (1)
96·3							67 (1)
69·8							59 (1)

figures given are from the second period when he was in a very grave condition indeed, and suffering from phthisis as well as diabetes. The ratio is very high for every step, so that it is clear that he had not the power of converting acetoacetic acid into oxybutyric acid to anything like the extent of the other patients ; it may be that this is connected with the large amount of sugar excreted, which would imply a high blood-sugar percentage. For the period of the table his sugar varied between 262 and 449 grm. Kennaway's case had also a high ratio, especially for the two last steps, and this patient was very near coma before the observations were made. In Joslin's case the figures are those for the last three days of life ; in two of them coma had been relieved by large doses of soda ; in the third it returned again and was again relieved, but the patient died next day. From Kennaway's paper (loc. cit.) I take the following :

Case.	Date.	β-ratio.	$\frac{\text{Acetoacetic}}{\text{Oxybutyric}} \times 100$	Remarks.
No. 5	5/vii	74·9	33	
	8 ,,	71·0	40	Coma.
	9 ,,	70·0	42	,,
,, 6	12/iii	72·4	38	8 days before coma.
,, 7	10 ,,	82·5	21	
	12 ,,	83·6	19	Coma.
		77·7	28	At autopsy.
,, 8	30/v	69·1	44	3 days before coma.
		68·4	45	At autopsy.
,, 9	31/i	70·3	42	Death without coma 31/i.
		68·1	57	At autopsy.

Cases 10, 11, 12, and 13, at autopsy only : 43, 49, 50, 48. In cases 5, 8, 9 the

acetoacetic ratio rises at coma or after death; case 6 is an exception in that the urine at the autopsy gave a ratio of 28, and case 7 is an exception having a singularly low ratio; but even here the ratio has risen at the autopsy. The number of times in which the acetoacetic ratio approaches or surpasses 40 is, to say the least, remarkable; in some cases it approaches Joslin's figures.

In a case published by Zaudy (142) the acetone was determined from 2/xi/00 to 11/xi/00, but the oxybutyric acid was not determined: the acetone calculated to acetoacetic acid was as follows:

4·9, 4·7, 9·1, 9·9, 12·8, 14·3, 13·6, 12·7, 14·7, 15·4, and the patient died in coma on 12/xi/00.

Geelmuyden (125) determined the 'acetone' and oxybutyric acid in a few coma cases. The acetoacetic ratios calculated from his results are:

A. A.	Man.	Aged 30, day of death	.	.	.	54
M.M.	„	„ 32, shortly before death	.	.	38
A. Z.	„	„ 47, day after death	.	.	.	37
P. F.	„	„ 28, seventeen hours after death.		99

In the case A. Z. the percentage of acetoacetic acid was higher on the night before death by 67 per cent., but unfortunately the oxybutyric acid was not determined.

3. Very few determinations of acetoacetic acid and oxybutyric acid have been made on the organs of people who have died of diabetic coma. Magnus-Levy made some approximations, but they cannot be regarded as of any value. Sassa (loc. cit.) determined the oxybutyric acid only. Geelmuyden (125) alone, as far as I can ascertain, has made such determinations, and in two cases only. The following table contains his results, and from them I have calculated the acetoacetic acid ratio:

100 grm.	Acetone mg.		Oxybutyric mg.		$\dfrac{\text{Acetoacetic}}{\text{Oxybutyric}} \times 100.$	
	A. Z.	P. F.	A. Z.	P. F.	A. Z.	P. F.
Liver	14·5	26·2	245	404	10·4	11·4
Muscle	34·8	53·8	110	176	55·7	53·8
Blood	50·6	53·2	119	244	74·9	38·4
Brain	51·4	—	146	—	62·0	—
Lung	50·3	—	77	—	115·0	—
Kidney	41·8	47·8	181	293	40·6	28·7

In the liver the acetoacetic acid is only about 10 per cent. of the oxybutyric acid; in the kidney, taking the mean value, it is 35 per cent. These results accord with the view, expressed before, that the liver is the chief site of oxybutyric acid production; the kidney after death must transform some acetoacetic acid to oxybutyric acid, for the urine, as we have seen, in nearly all cases of coma or imminent coma has a higher ratio than 35. As to the blood, no doubt that of P. F. was venous blood and that of A. Z. arterial. In the other organs the height of the ratio is surprising. The value for the lungs seems to indicate that there some oxybutyric acid is oxidized to acetoacetic acid, and this

is very probable, for the oxygen tension in the alveolar air in diabetic coma is much higher than the normal value.

We have now to account for the different behaviour of acetoacetic acid in the normal and depancreatized animal, and in the normal and severe diabetic man. Both the normal animal and man destroy the acetoacetic acid, and this is effected in the liver chiefly, by conversion to oxybutyric acid, which is completely burnt; the smaller part which escapes this fate returns to the blood and is there for the most part resolved into acetone and carbon dioxide, the acetone being partly burned and partly excreted by the lungs, while traces of the acetoacetic acid not detectable by ferric chloride are excreted in the urine. For even the liver of the normal animal or man is not able to reduce large doses of acetoacetic acid, as is shown by the experiments of Frerichs-Brieger (loc. cit.), who found acetone in the breath but could not detect acetoacetic acid in the urine by ferric chloride. They did, however, find what they thought was acetone in the urine, and the amount of it rose with rising amounts of acetoacetic acid. They found the acetone by distilling the urine, so that there is no doubt it was present in the urine as acetoacetic acid. The acetone formed will for the most part be excreted by the lungs, for it is a liquid of low boiling-point (56°) and has at 37° the very high vapour pressure of 380 mm. Thus the smell of acetone in the breath in such experiments as those of Frerichs-Brieger is accounted for.

In the depancreatized dog or in the diabetic man matters are wholly different, for acetoacetic acid is being produced by the cells of the whole body; even in the liver acetoacetic acid may be produced to a small extent, but there it will be reduced. The acetoacetic acid produced elsewhere which reaches the liver suffers the same fate as in the normal animal, but the diabetic liver cannot be assumed to have a greater power of reducing this acid, rather we must assume it to have a diminished power, so that a part of the acid escapes reduction and is returned to the blood, where it reaches such a concentration that it is excreted by the kidneys in quantities easily detected by the ferric chloride reaction, and is, as before, in part resolved into acetone which is excreted by the lungs. By increased production or by progressive failure of the liver to reduce it, or by both of these, the concentration of the acetoacetic acid will tend to increase in the blood and tissues until it reaches the concentration required in any particular individual to produce the phenomenon of coma. Take the case of Geelmuyden's patient A. Z., and assume that his weight was 66·2 kilos (10 st. 10 lb.); then we may estimate the acetoacetic acid of the whole musculature at 17·6 grm., that of the brain at 1·3 grm., that of the blood at 2·9 grm., and so on. Moreover, during life these amounts would be higher still, for, as we have seen, the tissues in the absence of oxygen convert acetoacetic acid into oxybutyric acid. When acetoacetic acid is given by mouth, or subcutaneously, or intravenously, even if it is allowed that such concentrations could be attained they could not be maintained for more than a brief period; but in the case of the diabetic on the point of coma such concentrations have been, as it were, in process of integration

for weeks, or months, and when the upper limit of the integration is reached coma appears.

On this view the formation of oxybutyric acid is merely a protective arrangement like the formation of glycuronic acid or of glycocoll; and the properties of this acid accord well with such a view. The properties referred to are these: it is less toxic than acetoacetic acid; it is a far weaker acid; its solubility and that of its salts is extraordinary. It is probably in virtue of the last two properties that the free acid can pass the kidney and appear as such in the urine.

In support of the theory of poisoning by acetoacetic acid I may refer to the experiments of Wilbur (143), who gave oxybutyric acid both in the free state and as sodium salt intravenously to rabbits: the toxic dose was very high for the salt, namely 5·8 grm. of oxybutyric acid per kilo of animal, and the symptoms were not those of diabetic coma. Again several people have examined the action of butyric acid on animals: Binz (144) states that 0·5 grm. per kilo of sodium butyrate given subcutaneously to dogs or cats caused sleep in fifteen minutes, and larger doses caused coma: Sternberg (145) showed about 1 grm. per kilo of the same salt given intravenously caused sleep in some cases and death in others. Marx (146) gave sodium butyrate to young and fasting dogs by mouth and intraperitoneally; to some of the animals sugar was given on one or more days before the butyric acid. The salt given by mouth was less effective than when given intraperitoneally; in the latter case it produced symptoms similar to diabetic coma, and when acetoacetic acid or acetone was found in the urine the state was more severe than when these substances were absent. When sugar had been given the butyrate was less effective. Marx concludes that in diabetic coma in man it is probably a specific toxic action of butyric acid and its derivatives rather than a general acid action. Of the sodium butyrate he says that the injurious action begins as soon as the substance and its products fail to be excreted as quickly as the substance is given, and that the poison which remains behind has a special avidity for the nervous system and attacks the brain and important life centres in an 'exquisite' manner. Ehrmann and Essen (147), who repeated Marx's experiments with very similar results, attribute the toxic action solely to the butyric acid, but it is worth while pointing out that in the case of a dog which had fasted three days and then received 4·2 grm. of the sodium salt per kilo intravenously they found small amounts of acetone and acetoacetic acid in the liver, blood, and urine. They state that butyric acid is a specific poison for the central nervous system. Loewy and Ehrmann (148) determined the blood carbon dioxide after poisoning by sodium butyrate: in normal animals they obtained 35·8 and 34·3 c.c. per 100 c.c.; when the dose of salt was insufficient to cause coma there was no decrease of the carbon dioxide; but when strong coma was produced the carbon dioxide fell to 29 in one case, 23 in another, and to 17 in a third. They found, however, that the blood carbon dioxide was lowered to 22 by sodium valerate, to 22 and to 18·8 in two experiments with sodium isobutyrate, but in none of these three animals

was there any coma at all. From these results they infer that the fall of the blood carbon dioxide cannot be the cause of the coma. Ringer (149) gave 10 grm. of butyric acid as sodium salt to a 13 kilo phloridzined dog sub-cutaneously and found it to produce a considerable rise both in the acetoacetic acid and oxybutyric acid : 20 grm. of the acid given in the same way to a dog of 11·2 kilos (1·8 grm. per kilo) also caused a large increase of the four carbon atom acids, but in this case there was deep coma and the animal died.

In these experiments with sodium butyrate it is impossible to deny that butyric acid ion is toxic; but it is absolutely certain that when this salt is given in the ways referred to acetoacetic acid is produced and must exert its toxic action, and in this connexion the observations of Marx and Ringer are very significant.

Attention may also be directed to the analogy in structure between aceto-acetic acid and salicylic acid. These two substances give the same kind of reaction with ferric chloride, because they both contain the same grouping— $C . OH = CH$—as is seen from the annexed formulae :

Salicylic acid   Acetoacetic acid
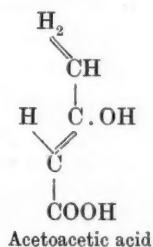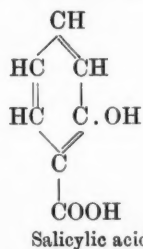
It was pointed out in connexion with Walter's work that free salicylic acid acted both as an acid and as a poison. Salicylic acid, even in the form of its sodium salt, is well known to be toxic—far more toxic than benzoic acid. Acetoacetic acid is toxic because of the group $C . OH = CH$—a group which it has in common with salicylic acid.

Enough has been said to put the theory of acid intoxication in grave doubt. But on the theory of poisoning by the acetoacetic ion, the fall of the blood carbon dioxide, and consequently of the alveolar carbon dioxide, and the fall of the blood alkalescence have to be accounted for. Beddard, Pembrey, and Spriggs (150) determined the carbon dioxide and also the alkalescence of the venous blood of diabetics both in coma and out of coma ; the former value they give in volume percentages and the latter as a fraction of normal alkali. For a normal person these values are 40 to 50 volumes and $N/30$ respectively. Putting $N/30 = 100$ their results may be expressed thus :

Diabetics
- Coma cases
  - CO_2 13·0, 13·1, 14·8, 17·6, 20·1, 22·5, 24·0.
  - Alkalinity 43·0, 66·7, 52·0, 75·0, 33·3, 50·0, 37·5.
- Not coma cases
  - CO_2 24·2, 33·4, 52·0.
  - Alkalinity 66·7, 93·8, 120·0.

N.B. Owing to the different method employed these alkalinity figures are

not comparable with those of Magnus-Levy given on p. 311. For example, the 361 of the latter corresponds to 273 on the above scale. The methods agree in showing a fall of alkalescence.

Out of coma the carbon dioxide and alkalinity correspond; but in coma this correspondence disappears. The same authors (151) show that the blood in coma can still take up large amounts of carbon dioxide out of the body by exposing the blood at 37° to a pressure of air containing 4 to 6 per cent. of carbon dioxide. In the body they show that the blood of a diabetic with a low carbon dioxide content can take up more carbon dioxide by ligaturing an arm when the carbon dioxide becomes normal or higher than normal (43·2 and 61·8); also when a patient whose alveolar air contained 3·19 per cent. breathed air containing 5·7 per cent. carbon dioxide and 84 per cent. oxygen his alveolar carbon dioxide rose to 4·83 per cent. All these experimental results of Beddard, Pembrey, and Spriggs appear to be entirely beyond dispute. With one point only in their interpretation of them (152) is the writer at variance. They say that 'during the prolonged and severe acidosis of diabetes the bases become combined with abnormal acids and are no longer available to combine with the normal acid products of metabolism; hence the range of " reactivity " to acids of the blood and protoplasm is diminished'. When the diabetic reaches this stage they deduce that the neutrality of the body is imperilled by smaller amounts of its own metabolic products, the cells are less capable of withstanding the metabolic acids and become more sensitive to all acids, and in the last stages the rising concentration of the acid ions in the blood and protoplasm progressively affects the activities of the cells so that less carbon dioxide is produced. Such an interpretation would not explain the production of coma by neutral salts such as sodium butyrate: it would not explain the occurrence of coma when the alkali of the food plus the alkali administered is sufficient to neutralize both abnormal acid and metabolic acids. The writer would ascribe the decreased activity of the cells and, when it occurs, the hyperpnoea to the increasing concentration of the acetoacetic acid ion alone; and he believes that it is this ion which acts, as Marx expresses it, in an 'exquisite' manner on the brain and important life centres. To explain the fall of alkalinity of the blood—a principal function of the alkali of the blood is to convey carbon dioxide in the form of bicarbonate to the lungs; if the amount of carbon dioxide to be conveyed by the blood diminishes alkali must necessarily disappear from the blood. That carbon dioxide which Beddard, Pembrey, and Spriggs found that diabetic blood of lowered alkalinity could take up was evidently not taken up by alkali—but probably by protein. Henderson's (loc. cit.) equation for the concentration of the hydrogen ion dependent on the free carbonic acid and bicarbonate in blood is

$$(\overset{+}{H}) = \frac{H_2CO_3}{NaHCO_3} \times \frac{3 \times 10^{-7}}{0.8} = \frac{H_2CO_3}{NaHCO_3} \times constant,$$

so that the reaction of the blood depends only on the ratio of the amount of free carbonic acid to the amount of bicarbonate; but the alkalinity depends on the

absolute amount of the bicarbonate. A similar statement holds for the phosphates. Now the blood has to keep a constant $(\overset{+}{H})$ concentration, so that if the free carbonic acid diminishes so must the bicarbonate, and if there is a fall in the amount of acid phosphate there must also be a fall in the amount of the alkaline phosphate.

In deep coma there is a small rise of $(\overset{+}{H})$ as is seen from the table on p. 388 and as Poulton (153) has shown. Poulton obtained two almost identical values, viz. $P = -7.19$ and $P = -7.18$, i. e. $(\overset{+}{H}) = 6.6 \times 10^{-8}$; in these two cases the alveolar carbon dioxide was very low, that is in the above equation H_2CO_3 must be very low and therefore the bicarbonate must be very low indeed. The base which disappears is most probably excreted in the urine. Poulton (loc. cit.) also attacks the theory of acid poisoning as a cause of diabetic coma on two grounds—he draws attention to the fact that patients may show a definite drowsiness and yet have a normal blood reaction and, again, that after a climb of 1,000 feet in thirty minutes, a ratio which entailed no distress, the blood of a normal man became distinctly more acid than that of a diabetic in the depth of coma a few hours before death.

The von Noorden Treatment.

There are several examples of this treatment in the cases described in this paper. It does not appear that the treatment increased the toleration of any individual for carbohydrate, nor did it reduce the amount of acids excreted after the period of dieting ended. Nevertheless, the treatment may be of use in cases where large quantities of sugar and acids are being excreted ; for in such cases there must be either an increased concentration of these substances in the blood and fluids in equilibrium with it, or there must be an increased volume of blood and the other fluids, or, finally, a combination of these conditions. All the experimental evidence points to the last of these as the actual condition in a severe diabetic. Now the semi-starvation of the von Noorden treatment enables the body to rid itself of this state of affairs. This is done partly by excretion through the urine and partly by utilization of the substances themselves, for it has been pointed out that it is certain that even a severe diabetic can utilize some sugar. Indeed, the writer would be inclined to regard the diabetic as an individual who utilizes sugar too slowly rather than as one who does not utilize it at all.

The Four Carbon Atom Acids of Diabetes and Sugar.

There have been many speculations as to the mode of action of sugar in inhibiting the production of these acids. In two of the latest of these the acids have been assumed to be normal intermediate products of metabolism and to

unite with the sugar or a simple derivative of it : the resulting combination is assumed to be easily catabolized, while its component acid is not; so that this union is a necessary preliminary step for the catabolism of the acids.   Thus Geelmuyden (124, 125) assumes that oxybutyric acid is a normal intermediate product of metabolism and that in the normal individual this acid unites with glycuronic acid, the conjugate so produced being catabolized ; in the diabetic this union does not occur and the oxybutyric acid is excreted.

Ringer (154) also assumes that oxybutyric acid is a normal intermediate product of metabolism and that it combines with glucose itself thus :

$$
\begin{array}{l}
CH_3 \\
| \\
H-C-O.\,CH.CH_2COOH \\
| \\
H-C-OH \\
| \\
HO-C-H \\
| \Big\rangle\,O \\
H-C \\
| \\
H-C-OH \\
| \\
CH_2OH
\end{array}
$$
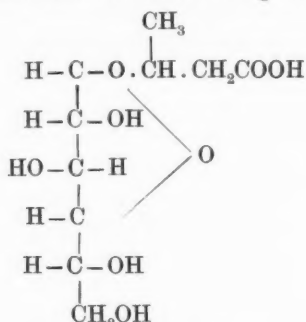
This glucoxide, for such it would be if it existed, is catabolized without production of acetoacetic acid.   In the diabetic its formation is impaired to an extent which varies with the severity of the disease.

The writer would assume that a small amount of acetoacetic acid is produced by the normal person from protein and also from fat, but this acetoacetic acid is all, or all but the merest trace, catabolized.   When the normal person is deprived of carbohydrate he does not at once catabolize protein and fat only, for his store of glycogen still supplies him with much carbohydrate ; but as this store begins to be depleted he uses more protein and fat and, therefore, produces more acetoacetic acid than he does on the carbohydrate-protein-fat diet.   As we have seen, this acid is difficult to catabolize, and therefore its presence is soon obvious in the urine and as acetone in the breath ; its amount increases as long as the individual continues on the carbohydrate free diet.   If the normal man starves instead of taking protein and fat only, the acid increases to a certain point and then remains fairly constant or diminishes, because as time goes on he catabolizes gradually decreasing amounts of fat and protein.   In the diabetic the oxidation of sugar is so slow that he must perforce catabolize far larger quantities of fat and protein than the normal man and therefore produce far larger amounts of acetoacetic acid.   Because of the difficulty of oxidizing it, and also because of its toxicity, he reduces it to oxybutyric acid.   He, however, does not oxidize the latter as a normal man would; the oxygen at his disposal is required for the oxidation of more fat and protein, so the oxybutyric acid is excreted.   Since his power of oxidizing sugar is only slowed up and not wholly abolished, by giving him large amounts of carbohydrate he can use sufficient to

spare his fat and protein; but the result of this is that sugar accumulates in the blood and tissue fluids to such an extent that the tension must be relieved either by giving the von Noorden treatment, by starving him, or by reducing his carbohydrate. This explanation is not sufficient perhaps to account for the very large amounts of the four carbon atom acids excreted in some cases. I would suggest, therefore, that in the severe cases where the patient must necessarily catabolize much fat there is also a small change in the character of the oxidation of the fat. Two modes of attack on the fatty acids have already been suggested, namely:

A. $HOOC . CO . CH_2 . CO . CH_2 ...$
B. $HOOC . CH_2 . CO . CH_2 . CO ...$
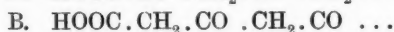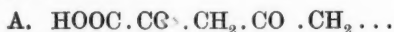
If we now assume that most fat is normally catabolized by method A, which does not produce acetoacetic acid, and very little by method B, which does produce acetoacetic acid, then in the case of the severe diabetic it is only necessary to suppose that more fat is catabolized by method B than is normally the case. An explanation of the action of large amounts of protein inhibiting acetoacetic acid production has already been offered.

Such a hypothesis as the one advanced has certain advantages : it does not require Rosenfeld's hypothesis that the fats burn in the fire of the carbohydrates : it does require the formation by the normal individual of such traces of acetoacetic acid as would account for the small amounts of acetone which can be obtained by distilling large amounts of normal urine : it does not require the formation of conjugates of oxybutyric acid with either glycuronic acid or glucose ; such conjugates may possibly be formed, but there is no necessity to assume that they play a primary part in metabolism—they would serve the usual purpose of conjugates and be protective only.

Effect of adding Certain Substances to the Diet of Diabetic Patients.

The effect of adding the following substances to the diet has already been considered : glucose per rectum, laevulose, Harden and Young's hexosephosphoric acid, glycocoll. In some experiments undertaken in conjunction with Bainbridge the effect of adding citric acid and glutaric acid to the diet of diabetic patients was studied. Satta (155) took 40 grm. of sodium citrate on a diet of meat and fat on two successive days and found that he produced smaller amounts of ' acetone' than he did in a similar experiment without taking citric acid. Our experiments were reported by Bainbridge (156) : they showed that 20 grm. of citric acid given daily for a week certainly reduced the amount of the four carbon atom acids excreted, but towards the end of the period the acid excretion tended to rise again, and I now believe the effect to be merely a transitory one. Baer and Blum (157) showed that glutaric acid given to a phloridzined dog caused a decrease in both sugar and acetone bodies. Ringer (158) was unable to confirm their results ; but Underhill (159), who did confirm their

results, explained the action of glutaric acid by supposing it to act in a manner analogous to the tartrates which act upon the kidneys so as to suppress the urine—the tubules, for example, are occluded by casts—and so there is a fall in the excretion of all the urinary constituents. Bainbridge and I tried the effect of glutaric acid, before the work of Ringer and Underhill was published, on two diabetics, and in one we found that the acid had a marked effect in reducing the excretion of oxybutyric acid when 8 grm. a day were given. This effect continued during the four days on which the acid was given and ceased when the acid was discontinued. In the second case the effect was scarcely marked.

Method for the Determination of β-Hydroxybutyric Acid.
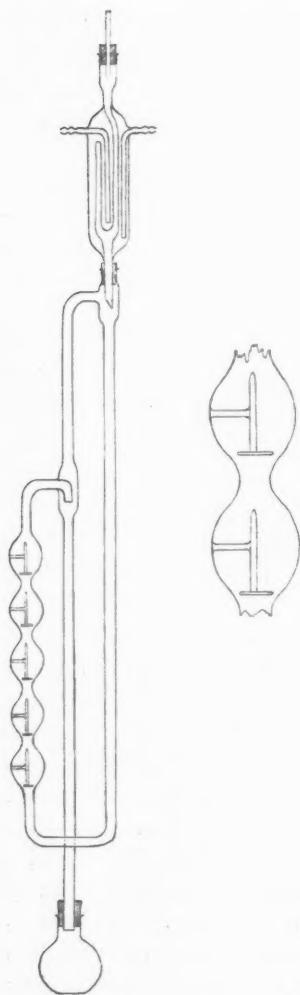
To 100 c.c. of the urine a 40 per cent. solution of ferric chloride is added a few drops at a time from a burette: the addition is stopped just before the liquid gives the reddish violet colour due to acetoacetic acid present in the urine. If this acid is not present a drop or two of ethyl acetoacetic may be added as indicator. The volume of ferric chloride required is read off: it is usually about 2 c.c. Now 500 c.c. of the urine are treated with the proportionate amount of ferric chloride, shaken well, and filtered from the precipitated ferric phosphate. The filtrate will be turbid at first, but after about 150 c.c. have passed through the paper it becomes as clear as water. The phosphate evidently adsorbs some colloid which causes an emulsion on extracting the original urine with ether. A filtrate obtained without excess of ferric chloride never emulsifies on extraction with ether. Of the filtrate $(250 + x)$ c.c. are taken for extraction, x being half the number of c.c. of ferric chloride added to the 500 c.c. of urine. To this 7 c.c. of sulphuric acid (1 vol. H_2SO_4 : 1 vol. water) are added. The liquid is poured into the extraction apparatus shown in the diagram: it should reach nearly to the top of the fourth bulb. Ether is now poured into the extractor until the liquid fills all the bulbs: the short-necked flask (250 c.c.) is nearly filled with ether and a few (five or six) pieces of broken porous plate are added to it, then it is fixed to the extractor by a good cork. A short surface condenser with a *wide* stem is

fitted to the top of the extractor: and the neck of the condenser is provided with a good cork through which passes a long straight tube to prevent all loss of ether vapour. The whole arrangement is held by two clamps on the middle tube and the flask is immersed deeply in water kept at a constant temperature of 65° C. by a thermo-regulator. At this temperature the ether boils very rapidly and, if good *porous* plate be used, regularly; the rate at which it passed through the liquid can be seen at the tube which projects into the enlargement of the middle tube, from the end of which it should pour in a thin stream. The extraction is practically complete in twenty-four hours, but I give it forty-eight hours. Of course, the duration of the extraction depends on the temperature of the bath: it can be much reduced by working at a higher temperature.

After forty-eight hours at 65° the flask is disconnected and the ether is distilled off with the flask in a bath at a temperature not exceeding 80° C.: above this temperature the acid is apt to form an oily anhydride, insoluble in water. When the ether has been removed a little water is added, the flask placed on wire gauze and heated to boiling: after one minute's boiling it is removed, allowed to cool, and when perfectly cold transferred to a graduated 50 c.c. flask, the extraction flask being washed out several times with a little water and the washings added to the graduated flask until it is filled to the mark. Now the flask is well shaken and its contents filtered through a good filter-paper till clear enough for the polarimeter. A 200 mm. tube is filled with the clear liquid and its rotation taken. The percentage of oxybutyric acid in the 50 c.c. of extract is $C = \dfrac{100a}{2 \times 24 \cdot 12}$: or 1 litre of the urine contains 4·146 a grm. of oxybutyric acid, a being the observed rotation. In addition to taking the rotation, 10 c.c. are always titrated with phenolphthalein and $N/5$ caustic soda, in order to serve as a check on the rotation value: 1 c.c. of $N/5$ NaOH = 0·0208 grm. oxybutyric acid. Therefore 1 litre of the urine contains 0·416 x grm. of oxybutyric, where x is the number of c.c. of $N/5$ soda required by 10 c.c. of the extract. The titration figure is always higher than the rotation figure because the extract always contains traces of other acids besides oxybutyric: it usually contains an infinitesimal trace of sulphuric acid, but it should never contain more. Examples of the difference between the rotation and titration results are given in Case VII.

To show that the value by rotation is not affected by the laevo-rotatory substance which is present in normal urine, a determination was made on a urine (*a*) treated as described above, (*b*) precipitated by basic lead acetate and ammonia: the results were identical, the rotation given by (*a*) being −2·55°, and that by (*b*) −2·57°.

To show that all the oxybutyric acid is obtained I give the following example:

A. 250 c.c. of a diabetic urine were extracted as above and found to contain 1·078 grm. by rotation.

B. 200 c.c. of the same urine were taken and 50 c.c. of extract from former determinations were added. This was extracted and polarized exactly in the same way as A. The 250 c.c. were found to contain 6·51 grm. oxybutyric acid.

The added extract was found, by determining its rotation directly, to contain 5·64 grm. of the acid, and 200 c.c. of the urine contain 0·86 grm.

(6·51 − 0·86) = 5·65 grm. oxybutyric acid.

To show the difference between a twenty-four hours' and a forty-eight hours' extraction of the same urine the following figures are given :

	Total oxybutyric acid grm.	
	Rotation.	Titration.
Extracted 48 hours	42·8	48·0
,, 24 ,, ...	41·6	47·3

The process has many advantages : two may be mentioned. No evaporation of the urine is required. No addition of ammonium sulphate as suggested by Magnus-Levy is required. Magnus-Levy states that the addition of this salt reduces the time required for an extraction. I have tested this and I give one example. Geelmuyden (160), in an excellent paper on the extraction of oxybutyric acid by ether, suggests the addition of a certain amount of the following mixture to the liquid to be extracted: 1,000 c.c. water : 100 c.c. concentrated H_2SO_4 : 930 grm. ammonium sulphate.

To 150 c.c. of oxybutyric acid extracts I added A. 125 c.c. water: B. 125 c.c. of the above mixture. Both were extracted and polarized as above: time of extraction 16 hours : bath 60°.

150 c.c. of extracts contained 5·50 grm. oxybutyric acid.

A. gave 5·07 ,, ,, ,,
B. gave 5·20 ,, ,, ,,

It is clear that the addition of ammonium sulphate is of no real advantage.

In conclusion, I must add that this study of acid production in diabetes mellitus is very incomplete. It is not sufficient to determine the sugar, nitrogen, acetoacetic acid, oxybutyric acid, and ammonia in a few cases. All these determinations should be made, and the blood and alveolar carbon dioxide, the bases and the acids of the urine, the nitrogen and fat of the faeces, should be determined as well in many cases. Not only so, the diet should be analysed with the view of determining the amount of bases and of acid-producing substances it contains, and, what is equally important, the nature of the protein which is being given to the patient. For example, in giving the diabetic bread made at this hospital one is on safe ground as regards the eggs and butter it contains, but on wholly unknown grounds as regards the diabetic flour used in its preparation. It is clear, however, that research on the scale suggested cannot be undertaken by one man.

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A CASE OF DIFFUSE FIBROMYOMA OF THE OESOPHAGUS, CAUSING DYSPHAGIA AND DEATH

By ARTHUR J. HALL

With Plates 24–32

IT has been somewhat the custom in former times to dismiss all growths of the oesophagus (with the exception of carcinoma) as mere pathological curiosities, having little or no clinical importance. The routine use of X-rays in the diagnosis of diseases of the chest and alimentary canal must make us alter our point of view in this, as in many other respects. Any pathological condition in the thorax capable of causing a shadow on the screen cannot be left out of consideration in reading the radiogram. As will be seen from what follows, the absence of any previous record of such a condition as was found in this case confused the diagnosis throughout. Probably a more accurate diagnosis could have been arrived at had fuller and more varied investigation been permitted. It is only fair to those who from time to time were in attendance upon the patient, to point out that the lack of such fuller investigation or of any serious attempts at relief must be entirely and solely attributed to circumstances over which they had no control and for which they were not responsible.

History of Case.

Miss X., aged 17 years.

Personal history. An only child, always delicate, had suffered from bronchitis and asthma; she also had some slight spinal curvature. Always constipated; menses not begun.

Family history. Her mother died of carcinoma mammae during the patient's illness: she was a highly neurotic woman.

Present illness. The first onset of symptoms connected with the oesophagus occurred in January, 1913, while she was living in Ireland. She was attended by Dr. Wright, of Dalkey, co. Dublin, who describes her symptoms as follows :

' For nearly a month, whenever she attempted to swallow she partly coughed up and partly retched up about half a pint of very frothy mucus, but the small amount of food she took never returned.'

Dr. Wright was unable at that time to find any physical signs of organic disease anywhere. As the dysphagic symptoms persisted he advised them to consult Sir Robert Woods, of Dublin, who made an exhaustive examination of the throat and larynx, but could not find anything abnormal there. At his suggestion an X-ray photograph (Plate 26) was taken in March, 1913, by Dr. Edward Watson, of Dublin. He reported the presence of a shadow

suggesting an intrathoracic growth in the posterior mediastinum, possibly due to enlarged bronchial glands.

On the strength of this report a provisional diagnosis was made of 'enlarged bronchial glands, probably tubercular'. The sputum was repeatedly examined for tubercle bacilli, but none were found.

The symptoms gradually disappeared, or, at least, improved so much that she did not require further medical advice for nearly sixteen months.

The difficulty of swallowing returned about June, 1914, whilst she was in Sheffield, and her medical man, Dr. Mylan, was called in. At that time she was complaining of dysphagia, cough, and vomiting, frequently bringing up a pinkish mucus.

Nothing definite was made out by physical examination, except that at one time the urine had a specific gravity of 1·032 and showed a trace of sugar, which disappeared entirely soon afterwards.

She lost weight rapidly, and during the next three months became gradually worse.

In August, 1914, she was screened after a bismuth meal by Dr. Rupert Hallam, of Sheffield, and he reported that there appeared to be a very narrow stricture in the upper oesophagus and another at the cardia ; above which latter all the meal appeared to be collected.

The presence of this lower shadow supposed to be due to the bismuth meal will be referred to later. Unfortunately no photograph was taken of the chest at that time.

On September 15, 1914, I was asked to see her in consultation with my surgical colleague, Mr. Graham Simpson, and her medical attendant, Dr. Mylan.

The consultation took place under somewhat unusual conditions. The patient's mother lay dying of cancer upstairs, and they were anxious that she should know nothing of her daughter's illness, or of the consultation. It was therefore held late in the evening ; we approached and left the house on tiptoe, and conversation took place in whispers only. It savoured more of a conspiracy than a consultation.

The history then given to us was as follows :

For the last few weeks she had been unable to swallow solids, and had had attacks of vomiting, which came on quite suddenly ; these attacks might occur night or day ; she would wake up with dyspnoea and immediately vomit up frothy mucus. She lost 6 lb. in weight in two weeks.

Present condition (September 15, 1914). She was extremely wasted and fragile, but smiling and bright, and seemed to enjoy being examined. There was a slight but distinct stridor with inspiration, audible at a distance from her. She did not complain of any pain. No enlarged glands could be felt. Tongue clean ; pharyngeal reflex present.

Chest. Some slightly impaired resonance over upper sternum in front ; stridor distinct here. Behind, a patch of impaired resonance opposite middle of left scapula with broncho-vesicular breathing. Slight spinal curvature lateral— mid-dorsal.

Abdomen not hollowed, no enlarged organs. Legs wasted. K.-j. sluggish. Urine 1·012, no albumin, no sugar.

She was given water in our presence and swallowed it, in sips, without difficulty. Given a biscuit, she ate it slowly, but seemed to swallow it quite well, with no 'hawking'.

After leaving the room, a few minutes later, she coughed or 'vomited' (?) one or two ounces of mucus and brownish material.

I regret very deeply the scantiness of this record, but, as mentioned above, the conditions of our visit precluded a thorough investigation of what was obviously a very difficult and obscure case. The patient was not in bed and the examination had to be made on the drawing-room couch.

In discussing the diagnosis we naturally considered the possibility of a purely functional disorder. There were several things in favour of this : her sex and age, the delayed onset of menstruation, the fact that she was an only child who had always been delicate and spoiled, the distressing illness of her mother, the disappearance of dysphagia for sixteen months, followed by its recurrence. Nor was her general appearance and behaviour altogether against such a view.

It was impossible to reconcile the apparently conflicting results of the two X-ray examinations.

If there was a shadow in the posterior mediastinum suggesting bronchial glands or an intrathoracic growth in March, 1913, why should the dysphagia and other symptoms disappear entirely until June, 1914 ; and why should their recurrence be associated not only with a stricture in the upper oesophagus, which might reasonably be due to the intrathoracic mass seen in March, 1913, but also with a shadow due to the bismuth meal collected just above the cardia ?

The whole condition was so puzzling and contradictory that we did not feel justified in forming any opinion until we had the opportunity of a thorough and complete investigation of the oesophagus by instrumental and X-ray methods.

In order that this might be done we advised that she should be removed to a private nursing home. This advice was, unfortunately, not followed. The mother died a few days later and the patient was sent away to the seaside in charge of a nurse. At this point my connexion with the case, during life, ceases. I never saw her again until the autopsy. For the remainder of the history I am indebted to others.

Further history. She remained at the seaside from the end of September until the end of November, 1914. During this time she had no medical attention. The nurse in charge kept a daily record of the quantity of food taken, of material ' brought up ', of her weight, and so forth.

From these records it is evident that although the dysphagia continued she was able to take sufficient nourishment to prevent any great loss of flesh. For some weeks her weight remained at about 5 st. 6 lb.—once it actually rose to 5 st. 8 lb., and at the end of her stay she had only lost 5 lb. ' Vomiting ' occurred regularly each night, the quantity varying from 1 to 12 (or more) oz., the material being of a creamy colour and not containing any food ; during the day she sometimes did not ' vomit ' at all, and when she did the quantity was usually rather less than in the night. It is described as of similar consistence and colour, and usually contained no food.

Towards the end of this period the nurse distinguishes in the records between ' expectoration ' and ' vomit ', but apparently the material brought up and measured by the former method was identical with that previously described as ' vomit ' and was merely brought up with less effort.

On a few occasions only the bringing up of this material was accompanied by pain, and once or twice food came with it. During the last week of her stay at the seaside the quantities brought up increased both day and night, averaging 15 to 20 oz. in the twenty-four hours.

At the end of November, 1914, she was removed to London and was under the care of Dr. Bourns, of South Kensington, who writes as follows : ' Sometimes while still taking food it would be returned, at other times it was kept down for as much as two hours. Only fluids or such things as thin corn-flour were attempted, and always the vomited food was churned up and frothy in appearance. The effort made at the moment of returning food suggested to me that it was not vomiting in the usual sense, but rather a regurgitation.'

In December she was X-rayed by Dr. Robert Knox, who has kindly allowed me to have prints of the results. Very large and definite shadows were found in the chest.

Owing to the increasing dysphagia during December, feeding by rectal

enemata was begun, and during the last six weeks of her life she was unable to swallow anything.

She was brought back to Sheffield shortly before her death, which occurred on January 19, 1915.

Permission was given for an autopsy which, with the assistance of Dr. Mylan, I made on the evening of her death.

Autopsy. January 19, 1915. The cadaver was an absolute 'skeleton'; the tissues quite dry and almost bloodless.

On opening the thorax and removing the heart and lungs an elongated smooth rounded mass was seen occupying the whole length of the posterior mediastinum.

At first sight its nature seemed doubtful, the lower third being swollen out into a rounded hard tumour-like mass (Plate 24). Further examination showed that it was continuous with the very small pharynx above and the small stomach below, and that it was the greatly enlarged oesophagus. It appeared to be distended with food, but this explanation seemed quite impossible as she had taken nothing by the mouth for six weeks before death. It was decided to fix the specimen in formalin solution before making any further examination.

As regards the other organs nothing abnormal was found except some infarcts in the lungs, and the general appearances associated with profound wasting.

I regret now that a more careful examination was not made of the whole intestinal canal, but so far as was seen there was no marked abnormality.

Description of oesophagus, naked eye. For purposes of description it may be divided into two parts (Plate 24): the upper and narrower, which runs vertically and ends rather more than half way down in a somewhat constricted 'neck', and the lower and much thicker portion, which runs obliquely to the left, passes through the diaphragm, and joins the cardia of the stomach.

The surface throughout is smooth and covered with thin connective tissue— there are no adhesions to neighbouring organs and there is no evidence of any inflammatory changes in its neighbourhood. It is remarkably firm and hard.

The greatest circumference is in the lower half (22 cm.), whilst at the point where it passes through the diaphragm it measures 15 cm.

The pharynx and top of the oesophagus are particularly small and the walls are extremely thin; in the hardened specimen the lumen barely admits an ordinary lead pencil.

The thickening of the wall begins somewhat abruptly. Its highest point is posteriorly where it reaches to a point 3 cm. from the cricoid. The sides of the tube are also thickened to almost the same height, but at the front of the tube where it is in contact with the trachea the thickening is entirely absent until a point 6 cm. below the cricoid. This open-fronted collar-like arrangement of the hypertrophied muscle is shown in Plate 24. The amount of thickening is least at the upper end and steadily increases downwards.

In this upper part it is in the form of rings due to furrows running an obliquely transverse course, upwards and to the left in front, downwards and to the right behind (Plate 24).

The tube rapidly gets thicker, and just below the bifurcation of the trachea

it has become a very hard cartilage-like mass with a circumference of 17 cm. at the widest part of the upper half.

The circumference of what will be referred to throughout as ' the upper swelling ' remains much the same for a considerable distance, but ends in a slight constriction or 'neck' at a point 18·5 cm. below the cricoid. This 'neck' measures about 14 cm. in circumference.

Immediately below the ' neck ' the oesophagus widens out rapidly into a large rounded mass measuring 21·5 cm. in circumference at its thickest part. It is hard and firm, smooth, with no adhesions or inflammatory changes. Longitudinally running fibres are seen on the surface (Plate 24). In the lower part where the thickness is getting less a line is seen running obliquely across. This is the level of the diaphragm. A small portion of the diaphragm remains attached to the left end of this line. Below the diaphragm the thickness gradually lessens until the cardiac stomach begins almost imperceptibly.

As will be described more fully later, the hypertrophied muscular coat projects as wedges into the anterior and posterior walls of the stomach for about 3 cm. The left edge of the anterior portion can be seen as an oblique vertical line just opposite the middle of the spleen (Plate 24).

The stomach is small and except at the cardiac end appears normal as regards musculature and mucosa.

On cutting into the stomach and passing a finger up to the cardia, the opening was found to have the form of a transverse slit with the two projecting wedges of the thickened muscular tissue in front and behind respectively. It felt very much like a normal multiparous os uteri.

The oesophagus was laid open by a coronal section from right to left (Plate 25). The walls are seen to be extremely thickened by an overgrowth of dense tissue extending the whole length of the tube. The growth is divided up into lobules and bundles by fibrous septa, and to the naked eye closely resembles the appearance of a section of fibromyoma of the uterus.

The actual amount of thickening of the wall varies considerably at different levels from above downwards, and also at different parts of the circumference in a horizontal plane. Thus it is least at the extreme upper end, where it is unequally distributed, being thicker on the right side and behind than in front and on the left. In the plane of the section (Plate 25) the lumen disappears from sight for about 4 cm. in the middle of the upper swelling. It is situated in a plane nearer the posterior surface in the piece marked A (Plate 25). When laid open it is found to be somewhat narrower in the transverse diameter than the lumen immediately above and below, but the chief narrowing is in the antero-posterior diameter. This flattening has been produced by the backward pressure of the anterior wall, which at this point is very much thickened.

Below this narrowed portion of the lumen, the part which was described above as the neck is situated. Here the lumen widens out again and becomes more rounded in shape, owing to the thickness of the walls being more uniform. About 3 or 4 cm. lower, the large lower swelling is reached, and is seen to be

made up of massive muscular walls having in places a thickness of almost 4 cm. The wall is thicker at the left and posteriorly. The lumen is here flattened out transversely, measuring 3 cm. in its widest part, but the anterior and posterior surfaces are almost in apposition. The mucosa is pushed up into rounded nodular swellings by the masses of muscular tissue, so that the surface, especially the posterior, has a mammillated appearance not unlike the surface of a cirrhotic liver. The lumen narrows down to 2 cm. at the cardiac orifice, which is situated nearer the right than the left border of the swelling. There is no appearance of stricture at the cardia. Immediately below the cardia and extending for 3·5 cm. into the stomach walls are two wedge-shaped prolongations of hypertrophied muscular tissue, one in the anterior, the other in the posterior wall. The mucosa over these is not thrown into rugae, as it is in the surrounding parts of the stomach (Plate 25 (8); also Plate 32, Figs. 1 and 2).

The mucosa of the oesophagus is smooth and glistening in all parts. There is some evident congestion in the upper and middle parts (Plate 31, Fig. 2), but nowhere is there any sign of erosion or ulceration, nor are there any rugae or irregularities except those described already in the lower part.

Measurements of Oesophagus.

	cm.
From cricoid to diaphragm	26·0
From cricoid to upper level of hypertrophy in—	
Anterior wall	6·0
Posterior wall	2·5
From cricoid to lower end of upper swelling (neck)	18·5
From diaphragm to lowest point of hypertrophied muscle in stomach wall—	
anteriorly	6·0
From cardia to lowest point of hypertrophied muscle in stomach	3·0
Greatest circumference of lower swelling	21·5
Greatest circumference of upper swelling	17·0
Greatest diameter of wall in lower swelling, nearly	4·0
Cavities:	
Diameter of lower cavity in widest part (side to side)	3·0
Diameter of cardia side to side	2·0
Length of the constriction in upper swelling	3·5

Looking back, it is obvious that with no previous experience of a similar condition as a guide an exact diagnosis during life was not to be expected.

For my own part, the brief single examination of the case in June, 1914, without having at that time seen any radiograms of the chest, and under the restricted circumstances mentioned in the history above, inclined me to the view of a purely hysterical condition or a possible 'achalasia'.

When the shadow was found by the X-rays in Ireland in 1913 a mediastinal growth was quite reasonably suspected, and putting everything together tubercular glands were thought the most probable condition.

In the second examinations by X-rays the existence of the stricture high up was noted, but the lower shadow was naturally thought to be a dilated oesophagus containing the bismuth meal.

At a still later stage, in the excellent radiograms taken by Dr. R. Knox (Plates 27–30), the patient was so ill and able to take so little bismuth food that an exact interpretation was impossible.

In a letter to me Dr. Knox writes:

'I looked upon the case as one of dilatation of the oesophagus attended by a degree of hypertrophy. Unfortunately the patient could only take a spoonful or two of the bismuth food, so it did not show the size of the oesophagus at all well. The examination was incomplete on account of the difficulty the patient had in taking food. . . .

'She was screened while taking the food, but it was so little that no conclusions could be drawn from the examination. The small quantity travelled very slowly down to the right side of the thorax.'

Interpreted by the condition found at autopsy, Plate 27 (taken in December, 1914, by Dr. Knox, before the bismuth meal) shows (i) the upper swelling of the oesophagus bulging to the right opposite the fourth, fifth, and sixth ribs, (ii) the narrower lower end of this opposite the seventh rib, (iii) the lower swelling both to the right and left of the vertebral column, (iv) the heart's apex lifted up and separated from the diaphragm by a clear space.

Plate 29, taken after the bismuth meal, shows very beautifully the small quantities of bismuth forming irregular shadows in the lumen of the lower swelling, seen in the right ninth and tenth intercostal spaces. These darker shadows give a very clear idea of the relative proportion of dilatation to hypertrophy. The upper irregular one is continuous upwards with a dark shadow of larger size opposite the eighth interspace, which is probably bismuth collected in the more circular lumen corresponding with the 'neck' (Plate 25 (6)).

Histological Examination. The appearance of the thickened walls to the naked eye suggests that seen in the typical 'fibromyoma' of the uterus. This is due to the lobulated masses separated by connective-tissue septa, with fibres running in various directions and forming irregular whorls, particularly seen in the thickest parts of the upper and lower swellings.

Microscopic examination confirms this similarity. A section taken through the upper part just above the constriction of the lumen shows that the whole increased thickness is due to excessive myomatous overgrowth, which occupies the position of the internal circular muscular coat (Plate 31, Fig. 1; also Plate 31, Fig. 2). The epithelium is normal in appearance (Plate 31, Fig. 1, *a*); the mucosa shows extreme congestion of vessels and here and there some small round-celled infiltration (Plate 31, Fig. 1, *b*); the muscularis mucosae and submucous coats appear normal (*c* and *d*).

The circular muscular coat, which is normally rather narrower than the longitudinal, here overshadows everything else, although the point at which this section is taken is one of the thinner parts of the wall. The muscular fibres are entirely non-striated. This is a point of some interest which will be referred to later. They do not all run circularly; many bundles run in a horizontal plane from the external wall towards the lumen, whilst other bundles take a slanting course so as to have in many places a pennate arrangement. Sometimes the bundles alternate in direction in a surprisingly regular manner, groups of circular ones being separated from each other by horizontal pin-like bundles. From

relative quantities of cell substance and nuclei, it seems evident that there is a considerable amount of supporting material binding together the muscular fibres, although it is difficult, as in fibromyoma of the uterus, always to distinguish which is which. The tissue is divided into larger lobules by well-marked connective-tissue septa which contain blood-vessels. Numerous blood-vessels are also seen in the lobules of muscular tissue themselves. Outside this abnormal circular muscular coat, a thin layer of longitudinal fibres is seen. This layer is here not thicker than the muscularis mucosae, and consists also of non-striated cells only.

Section through the very thick muscular mass in the lower swelling shows similar appearances, but the fibres here run in more irregularly directed bundles. In many parts it appears as though the muscular fibres had degenerated, atrophied, and disappeared, leaving only a fenestrated supporting tissue, with branching processes joining it together. A section through the wedge-like process in the upper part of the stomach shows a normal gastric mucosa with peptic glands, a normal mucosa, and the underlying mass of fibromyomatous tissue replacing the circular coat as in the oesophagus (Plate 32, Fig. 1).

So far as the above sections are concerned the findings are definite and simple. Sections taken however through the upper part of the upper swelling (Plate 25) at and around the site of the haemorrhages seen there show changes which have been somewhat difficult to interpret.

The mucous and submucous coats are normal, as in the previously described sections from other parts. The mass of abnormal growth still limits itself entirely to the site of the circular muscular coat, but its character has undergone considerable changes.

In places there is effusion of blood into the tissues. In general characters it still consists of fibromyomatous tissue, but the typical unstriped muscular fibres are less closely packed, their outline is less clearly marked, and the number of nuclei visible in any field is diminished. Here and there are seen rounded bodies of larger size looking with a low magnification like large round cells or striated muscular fibres cut across. On examination with higher powers these round bodies are seen not to be normal cells. Most of them show no nucleus, whilst a few show a nucleus of relatively small size, such as that of an unstriped fibre cut across, usually excentrically placed.

That these rounded bodies are really cross-sections of some kind of elongated cell or fibre is seen when they are cut obliquely or longitudinally. They have then a somewhat curious fusiform outline, and are not of regular contour, but are swollen in the more central parts. The swelling is usually spherical and causes the fibre to bulge out; it stains with the same dye as the rest of the fibre, but is somewhat deeper in colour. It is also more dense in structure than the rest of the fibre.

Most of these swollen fibres appear to have no nucleus; in some there is an elongated nucleus similar to that of an unstriped muscle cell. In some the cell ends in an ill-defined branching process.

It seems clear that the round bodies previously described are really transverse sections of these swellings in the fibres.

Professor J. S. C. Douglas, who has kindly looked over these sections for me, thinks that the changes here described are probably degenerative in nature, and that they may be a condition occurring in unstriped muscle, not altogether dissimilar from Zenker's degeneration in striped muscle.

This curious histological appearance, found only at one part of the specimen, presents some interest in connexion with the question of a possible sarcomatous development in the myomatous tissue, and will be referred to later.

The Question of Compensatory Hypertrophy.

In trying to find an explanation of this case, the first point to settle is whether or not the hypertrophy has been secondary to obstruction.

Such compensatory hypertrophy, as we know from cases of cardiospasm or achalasia, does not necessarily connote an organic stricture ; it may arise from a functional one. It is obvious that, whether organic or functional, a stricture of the oesophagus sufficient to cause such extreme hypertrophy must have indicated its presence by more or less dysphagia for some considerable time before its development. That in this case it did not do so, the evidence that we have is very clear.

The patient never suffered from dysphagia prior to January, 1913. Dr. Wright, of Dalkey, who was for many years a personal friend of the family and their medical attendant, assures me that he had never heard of anything of the kind previous to this date, and the history obtained from her friends fully confirms this. She had been subject to asthma, but she had never had any difficulty in swallowing. Yet, within two months of this first attack of dysphagia, a radiogram, taken by Dr. Watson, of Dublin (Plate 26), showed the presence of a shadow sufficient to warrant at that time a provisional diagnosis of intrathoracic growth.

Comparing this photograph (Plate 26) with those taken in December, 1914, by Dr. Knox (Plates 27, 28, and 29), and with the oesophagus found at autopsy a few weeks later (Plates 24 and 25), it is obvious from the general outline of the shadow that, *within two months of the onset of symptoms of dysphagia,* the oesophagus was almost, if not quite, as large as at the time of death. Unfortunately the original photograph is not very clear for purposes of reproduction, but the following points can be distinguished in Plate 26 :

1. A shadow to the right of the vertebral column about the level of the fifth and sixth ribs. (This appears to be the shadow diagnosed as an intrathoracic tumour or mass of bronchial glands, and due to the upper swelling of the oesophagus.)

2. The right margin of a lower swelling just above the diaphragm on the right side.

3. An abnormal position of the apex of the heart, lifted up from the diaphragm and separated from it by the distance of an intercostal space. This feature is equally well shown in the later radiograms (Plates 27, 28, and 29).

4. A shadow due to the left margin of the lower swelling between the heart and the left side of the diaphragm (also seen in Plates 27, 28, and 29).

It is impossible to think that a hypertrophy of this extent, involving not only the lower but also the upper part of the tube, could have arisen as a compensatory mechanism after only two months' slight dysphagia. We must therefore conclude that the enlargement of the oesophagus already existed at the time of onset of her symptoms, and was not due to a pre-existing obstruction sufficient to produce symptoms.

That the hypertrophy is not primarily compensatory in character is confirmed by a study of the specimen itself. The only part of the tube which shows sufficient narrowing to be called a stricture is in the upper swelling, whilst the bulk of the hypertrophy is below this, in the lower half of the tube. Below the upper swelling there is certainly no organic stricture.

On the other hand, the obstruction causing the lower swelling may have been functional, at the cardiac orifice, as in cardiospasm (achalasia). Against this view there is much to be said. In most cases of cardiospasm, dilatation is marked, or even extreme, and the ratio of dilatation to hypertrophy is greatly in favour of the former. Several cases have been recorded in recent years. In some it is difficult to estimate the exact ratio of dilatations to hypertrophy owing to the absence of any measurements and the use of indefinite terms, such as ' great' or ' excessive ', in describing the size of the lumen or the thickness of its walls. Occasionally, however, an illustration in the text, or a statement as to the thickness of the walls, gives definite information on this point.

Thus, Sippy (1), describing a specimen removed from a woman, aged 40, who died with a dilated oesophagus after about five years' dysphagia, states that ' at the point of greatest dilatation the circular fibres alone were 0·5 cm., the longitudinal fibres 0·2 cm. in thickness. From here upward the hypertrophy gradually diminishes.' This was a case of idiopathic dilatation due to cardiospasm.

Kinnicut (2), in a case in which dysphagia had existed for twenty years, off and on, states that the greatest thickness of the muscular coats was 0·5 cm. Zenker and v. Ziemssen (3) speak of a thickness of 0·5 cm. as ' great hypertrophy '.

Much the same holds good for such specimens as I have been able to see or hear of in the pathological museums of this country. In the museum of St. George's Hospital there are two specimens of simple muscular hypertrophy of the oesophagus without discoverable cause. I have had an opportunity of seeing these, and the walls at their thickest point do not exceed about 0·5 cm. across. From the P. M. records of the London Hospital Dr. H. M. Turnbull kindly informs me of two records of ' idiopathic hypertrophy ' of the oesophagus. Each is described as ' great hypertrophy '. Whether these specimens are pre-

served in the museum or not I cannot say, and there is no statement in the record sent me as to any actual measurement of the walls.

Apart from these, in answer to inquiries, I have not obtained any report of existing specimens of oesophageal hypertrophy. It seems fair to assume that a purely compensatory hypertrophy of the oesophagus, however great the dilatation, rarely exceeds 0·5 cm. in thickness, or thereabouts.

A hypertrophy such as this specimen shows, in which the muscular walls measure more in diameter than the lumen of the tube at its greatest dilatation, is contrary to all experience in cases of cardiospasm.

Again, in this specimen the hypertrophy does not cease at or above the cardia. Seen from without (Plate 24), it is impossible to say exactly where the cardia is situated, for it lies concealed in the lower part of the larger swelling. Seen from within (Plate 25), the orifice is quite distinct, measuring 2 cm. across, and the hypertrophied mass continues for 3 or 4 cm. into the stomach walls below. Lastly, in this specimen the sites of the narrowest parts of the lumen are also the sites of greatest overgrowth of walls, and the narrowing is really a flattening in one plane due to the pressure inwards of the thickened walls.

The points against this being a compensatory hypertrophy may be summed up as follows :

1. Within two months of the onset of dysphagic symptoms a radiogram shows intrathoracic shadows corresponding in size and position with those taken a few weeks before death.

2. The bulk of the overgrowth is below the only part of the lumen which may be termed a stricture.

3. The lower extent of the growth does not cease at the cardia, but continues for 3 or 4 cm. into the anterior and posterior stomach walls.

4. The ratio of dilatation to hypertrophy usually found in cases of cardiospasm is in this case reversed.

5. The narrowest parts of the lumen correspond with the thickest parts of the walls ; if it is compensatory it has defeated its object by causing, instead of relieving obstruction.

It may seem unnecessary to emphasize this point, seeing that a comparison of this specimen with those of compensatory hypertrophy shows the differences quite clearly. It must be remembered, however, that dilatation with secondary hypertrophy is the common condition, and the one which in this case was naturally suspected during life in spite of many anomalous features.

As the theory of compensatory hypertrophy is obviously impossible it is necessary to consider some alternative. Of these there seem to be only two. It might be (1) a congenital hypertrophy of the muscular coats, a mal-development, or (2) a diffuse neoplastic growth of later origin.

1. *Congenital Hypertrophy.*

Various forms of congenital mal-development of the oesophagus are referred to in all text-books of pathology. With most of the varieties this case has nothing to do, and they need not be considered here. The only forms that concern us in connexion with this case are the alleged cases of congenital stenosis and congenital dilatation.

It does not seem necessary to consider the former at length; a congenital stenosis which produces no dysphagia for sixteen years is hardly a stenosis at all. As regards the cases of congenital dilatation, however, there seemed at first sight a hope of enlightenment, for in most of the text-books there is added the words—'a kind of forestomach! (*Vormagen*).' The constancy with which this formula is exactly repeated in successive text-books is a little suspicious! The evidence upon which it is based seems to be a single specimen described by v. Luschka (4) in 1868. It was found in a woman, aged 50, who since girlhood had been able to return her food at will.

Measurements are given which enable us to compare the relative amount of dilatation to hypertrophy. Thus the circumference of the tube at its widest part was 30 cm., whilst the greatest thickness of the hypertrophied wall was 0·45 cm. The diameter of the lumen at its widest part must therefore have been between 8 and 9 cm. with a maximum wall thickness of under 0·5 cm. That is a ratio of dilatation to hypertrophy of about 17 to 1. (In my case the ratio is nearly 1 to 1·5.) The plate which accompanies the account of v. Luschka's case shows two swellings in the oesophagus, an upper smaller and a lower much larger; so that from the external surface its appearance is at first sight not dissimilar to that seen in my case (Plate 24). But there is one important difference. In v. Luschka's specimen the lower swelling narrows down at the point of entry into the stomach to an apparently normal width, whilst in my specimen (Plate 24) the swelling extends into the upper part of the stomach and the circumference at this point is as great as in the widest part of the upper swelling. I have mentioned the account of this specimen in some detail because, as I said before, it is referred to in most of the text-books as the example of congenital dilatation of the oesophagus (a forestomach), and because it gives details of measurements. v. Luschka himself remarks upon the uncertainty of its origin and says that the evidence of its being congenital is merely based upon the duration of symptoms since youth. In the light of recent X-ray work in connexion with dysphagic cases, it seems quite likely that this was primarily a case of achalasia with secondary dilatation and compensatory hypertrophy. The existence of congenital dilatation becomes, therefore, very doubtful.

Having thus failed to find any record of a purely hypertrophic mal-development of this region, one naturally turns to other parts of the alimentary canal to see if anything comparable occurs in them.

The best known example of such localized and limited hypertrophic mal-development is that first described by Hirschsprung (5), now generally known as megacolon congenitum, or Hirschsprung's disease. The three cases described by him occurred in infants, two of them living only a few months, the third only a few hours. Hirschsprung's original suggestion that the condition was really congenital was based upon the two former cases and was confirmed later by the third.

In these specimens, of which measurements are given in full, it is obvious that, allowing for the size of the infantile organs as compared with those of an adult, the actual hypertrophy of the walls of the colon is very great; thus in one specimen it reached 0·3 cm. in thickness. In one respect, however, these specimens of intestine described by Hirschsprung differ from this specimen of oesophagus: in the former all the coats were thickened—mucous as well as muscular; in the latter the hypertrophy is entirely limited to the tunica muscu-laris; the mucosa shows no enlargement. It is interesting to note that in his third case the change reached up a short way into the ileum just above the ileo-colic valve, just as in my specimen it extends beyond the cardia into the stomach.

At the time of Hirschsprung's paper no similar case had been described, and his apology for presenting something hitherto unknown is so apt to the present circumstances that I give a translation of it, although it does but scant justice to the original :

'(5) The question then arises whether such a luxuriant overgrowth could be confined to so comparatively short a length of intestine, actually forming so limited a portion of the body. *A priori* one would be inclined to look upon such a limitation as in a high degree improbable, and this is confirmed by our finding in the literature isolated accounts of analogous congenital abnormalities elsewhere in the digestive canal. I refer you to the congenital dilatation of the stomach which Rokitansky described (*Lehrbuch der path. Anat.*, 1861, Bd. iii, S. 148) and to the primary total dilatation of the oesophagus which, according to Eichhorst (*Handbuch*, 1885, Bd. ii, S. 48[1]), is frequently found of congenital origin. Whether, however, the dilatation in these cases was associated with hypertrophy of the wall in some or all its layers, I have no evidence to show ; I must there-fore not assert that the analogy with the findings in the lower parts of the alimentary canal is complete in this respect. If we seek for allied conditions in other viscera of the body, the literary harvest appears a rich one, and there are not many inner parts which have not been found at birth to be overdeveloped. In Förster (6) one finds the richest contributions to our know-ledge on this subject. He says : " Congenital hypertrophy is found in all the inner parts—in the brain, the spinal cord . . . further as malformations in the larynx, tongue, liver, spleen, thyroid, suprarenals, kidneys, testes, ovaries, mammae, uterus, and heart." The intestine is not named in this collection, but

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[1] This reference is to v. Luschka's case mentioned previously.

it is difficult to see why the intestinal canal should not be subject to the same morbid processes as the majority of the other internal organs. Here is an empty space which my cases can bravely fill.'

It is somewhat tempting to apply the same form of argument to the present case and to say that although congenital hypertrophies of the oesophagus have not been previously recorded there is no inherent improbability in their occurrence, and that here is an example to prove it.

There are two obvious difficulties in such a view. In the cases of megacolon symptoms of impaired function showed themselves soon after birth; in my case no symptoms whatever occurred until 16 years of age. Such a difference might conceivably be owing to the different functions of the two parts of the alimentary canal, but it is a real difficulty. The other point is the limitation of over-growth in this case to one layer of the tube—the tunica muscularis, and the complete absence of hypertrophic change in the rest.

I am not aware whether in any recorded case of megacolon congenitum the hypertrophy has been thus limited to one coat. In Hirschsprung's original cases it was not so.

2. *Diffuse Neoplastic Growth.*

Microscopically the specimen consists of unstriped muscular cells, together with a certain amount of fibrous tissue, and belongs to the group of leiomyomata. As is well known, leiomyomata are not very rarely found in the muscular coats of the alimentary canal, including the oesophagus. They may be single or multiple. As a rule their discovery is an accidental one at autopsy and no symptoms have been recorded during life. Sometimes, either on account of their size or of their pedunculated nature, they have produced mechanical obstruction and dysphagia.

Inquiries made from the curators of the leading pathological museums in the United Kingdom show that such specimens exist in several. Most of them are only of small size (1 or 2 cm. long). At University College Hospital there is a larger one, No. 1527 B. It is described as 'ovoid, 3 inches long, lying in dilated tube causing erosion and laying bare some of tracheal rings. No history.' Hilton Fagge (7) recorded a specimen of this kind: 'Egg-shaped, 2 in. long × 1 × 1¼. It was below the bifurcation of the trachea, underneath the mucosa, which was movable over it. There was no dysphagia.'

Coats (8) reports a pedunculated leiomyoma which caused death by obstruc-tion. It measured 4¾ in. long by 2 in. in circumference and was attached by a narrow stalk. The lower end reached to the cardia.

Eberth (9) described a specimen in a female, 50 years of age, in whom there were no symptoms during life. It was situated just above the cardia: arose in the circular muscular fibres involving the posterior wall only, and measured 9·1 cm. long × 3·5 cm. thick × 11·9 cm. broad.

These isolated examples of myoma of the oesophagus, of somewhat large dimensions, are the exceptions which prove the rule laid down in most works on pathology, that leiomyomata of the oesophagus are seldom larger than a bean.

A diffuse myomatous growth in the oesophagus extending into the walls of the stomach is not described in any work to which I have had access. And yet the conditions in this specimen—the massive lobulated overgrowth of unstriped muscular tissue spreading irregularly along almost the whole length of the tube ; the division into two masses ; the actual displacement upwards of the heart ; the occlusion of the canal by inward growth of muscular tissue ; the extension of growth below the limit of the cardiac orifice—all these suggest spontaneous overgrowth such as occurs in myoma.

If we turn to the chief seat of myomatous tumours, namely, the uterus, the literature on the subject is very abundant.

Myomata in this organ are, as a rule, circumscribed, but cases occur occasionally of so-called ' diffuse fibromyoma ' in which the growth has no definite boundaries, but is diffused throughout the whole organ. That being so, there is no *prima facie* reason why a similar diffuse myomatous growth should not take place in a portion of that system, viz. the alimentary canal, which, after the uterus, is the commonest site of myoma.

A common feature of uterine myomata is multiplicity, and this tendency is also not uncommon in cases occurring in the alimentary canal. In the present case there is a suggestion of such a tendency in the presence of two swellings or centres of chief growth in the diffused mass (Plates 24 and 25).

Again, uterine myomata may be polypoid or they may not. This difference probably depends upon simple factors of position and physical conditions of accidental origin. As a rule the circumscribed leiomyomata of the oesophagus are polypoid. The absence of any polypoid development in this case may be explained by its diffuse circular development—there is no normal thin wall from which it can drag downwards and become polypoid.

Conclusions.

The conclusions upon which the diagnosis of diffuse fibromyomatous growth of the oesophagus are based are :

1. The general naked-eye appearance, which resembles that of a uterine fibromyoma

2. The histological structure.

3. The limitation of growth to the muscular coat.

4. The sharply defined upper and lower margins—the latter not limited by the cardiac orifice, but extending some way into the stomach.

5. The replacement of the normal striped muscle in the upper oesophagus by unstriped muscular tissue.

6. The actual compression of the lumen by encroachment of the growth.

7. The occurrence of analogous cases of diffuse myomatous growth in the uterus.

There seems little or no evidence to show at what period of life the ordinary leiomyomata of the oesophagus arise, and it seems impossible to form an opinion as to when the growth in my case began. We know that within a few weeks of the onset of symptoms it was very extensive. Its possible congenital origin has been considered previously, and the verdict is 'not proven'.

The question naturally arises as to whether the onset of symptoms in this case may have coincided with a more rapid development of a previously existing growth. Such rapid development might be occasioned by what was innocent becoming for some reason malignant. It is well known that this does happen in uterine myomata and that sarcomatous changes in them are not uncommon. The frequency of this occurrence is somewhat variously estimated by different observers, but may be taken roughly at about four per cent. of cases coming to operation.

Griffith and Williamson (10), in recording such a case, formulate four different conditions under which it may occur:

1. There may be present in the same uterus two entirely separate and distinct tumours, the one a sarcoma, the other a fibromyoma.

2. A sarcoma may originate in some more or less distant part of the uterine wall and subsequently invade a fibromyoma.

3. A sarcoma may arise *de novo* in a pre-existing fibromyoma: a new growth within a new growth.

4. Possibly the cells of which the existing fibromyoma is constituted may assume malignant characters.

There is nothing in this specimen which could be included under the headings (1) or (2). It is also clear from the microscopic examination of sections taken from most parts of the growth that the cells do not show any malignant characters histologically, and that to most of the growth the condition described under (4) could not apply. But with regard to the third heading, sarcoma developing in some part of a pre-existing fibromyoma, there are certain features in this specimen which are at first sight a little suggestive.

In the upper part of the upper swelling (Plate 25) there is a limited area in which there are a few small haemorrhagic foci. Can this be a seat of sarcomatous change? In uterine myomata becoming sarcomatous the area of such change may be very limited, and haemorrhages into the substance are not uncommon.

Judging by the literature, sarcoma of the oesophagus is amongst the rarest of diseases. v. Hacker (11), in 1909, was able to collect 21 cases of sarcoma of the oesophagus recorded up to that date, together with four cases occurring in the hypopharynx. From a review of these, it appears that, like carcinoma, it occurs more commonly in the later decades of life, 40–70, differing in this respect from sarcoma in general. Three-fourths of the cases occurred in males. The most common site of origin was in the thoracic oesophagus, usually in the lower part.

In contrast to carcinoma there is no special predilection for the narrower parts of the tube. It may occur as either (1) a circumscribed growth, or (2) as a diffuse infiltration of the walls, or (3) both forms may be combined. As a rule the circumscribed variety projects into the lumen of the tube, forming a polypoid swelling.

The infiltrating form may lead to thickening of the walls or to the formation of knobby palisade-like projections of the surface. From this thickened wall polypoid or cauliflower-like growths may push into the lumen. In some cases ulceration occurs, in others the mucous surface remains unbroken, as in Ogle's case (12).

The growth may involve the circumference of the walls completely, as in cases recorded by Rolleston (13), Shaw (14), and Starck (15), or it may nearly do so. As a rule a part of the circumference is free. In a considerable number of cases the anterior wall has been chiefly involved. Some are described as firm, hard tumours, others as soft or even of pulpy consistence. The latter tend as elsewhere to destruction of tissue and to extension by metastasis. As regards the histological structure, many of the cases are somewhat incompletely described, and it is difficult to form an opinion as to their exact nature.

Amongst the varieties described are lymphosarcoma (16) (one case), and melanosarcoma (17) (one case). The others include round-celled, spindle-celled, and mixed round- and spindle-celled.

It is obvious that in the specimen here recorded there is very little which fits in with the cases of sarcoma hitherto reported. Most of them occurred in much older persons, usually between fifty and seventy. Most of them are described as arising in the submucosa: metastases occurred in several. Ulceration of the mucosa, or softening of the growth, or polypoid projection into the lumen was common.

On the other hand, some of the infiltrating circular sarcomata, described as of firm consistence with little tendency to metastasis and involving considerable lengths of the tube, approach in general conditions more nearly to my specimen than anything else I have found in the literature.

As regards histological structure the cases of typical round-celled sarcoma, or myeloid, or lymphosarcoma do not enter into the question, but the exact nature of those described as leiomyosarcoma and rhabdomyosarcoma seem to be somewhat uncertain, and although their similarity to my case is not a close one, yet they resemble it to some extent. Two of these cases are described as rhabdomyosarcoma, the tumours containing and arising in striped muscle.

Wolfensberger's (18) case shows from the photographic reproduction a diffuse warty nodular surface of the oesophageal lumen, not altogether unlike the inner surface of the lower swelling in this case (Plate 25). A sectional view, however (loc. cit., Fig. 21, p. 508), shows that there is really no comparison between the two.

Glinski's (19) case was a polypoid growth at the lower end of the oesophagus, consisting chiefly of spindle cells with connective tissue and bundles of striped

muscle fibres. The presence of striped muscular tissue so low down in the oesophagus is somewhat unexpected, and suggests an original developmental anomaly with secondary sarcomatous changes. Neither of these specimens contained any unstriped muscle cells.

There only remain two other cases in v. Hacker's list. These seem to be somewhat allied to the condition found in my specimen. One of them, recorded by Howard (20), is described by him as a 'primary myosarcoma of the oesophagus with metastases in the stomach and neighbouring lymphatic glands'. The primary growth began 12 cm. above the cardia, but the actual form, extent, and situation as regards the tube, it is impossible to picture from the description he gives. The growth seems to have arisen in the muscular coat, and although the mucosa was ulcerated it appears not to have been invaded by growth. The bulk of the growth consisted of large fusiform sarcomatous cells and non-striped muscle cells. Howard is satisfied that he could distinguish gradations from the latter to the former.

The secondary metastatic growth in the stomach measured 7 cm. across, and had a similar structure.

Eppinger's specimen (21), which formed a polypoid tumour projecting into the lower part of the oesophagus, measured about 10 cm. in length. It was found at autopsy in a man of seventy. In structure it showed large spindle cells together with normal unstriped muscle cells. It is described as a leiomyosarcoma. It seems possible that these two specimens are both examples of sarcomatous changes in leiomyomata of the oesophagus.

The final appeal in deciding whether my specimen is undergoing sarcomatous change or not must necessarily rest with the interpretation of the histological appearances found in the suspected area. Judged by the ordinary standards the answer seems to be in the negative, but, as one knows in cases of myomatous growth, the line of demarcation between an unstriped muscle cell and a spindle cell of sarcoma is often difficult to draw. There are, however, other facts which, although merely negative, yet make sarcoma unlikely.

First, there is complete absence of metastasis. Secondly, if we assume sarcomatous change as the cause of increased activity which determined the onset of symptoms, the sarcomatous focus should have advanced much further than it did during the remaining two years of life.

It seems, therefore, that this specimen is best described as a diffuse fibro-myoma of the oesophagus—leaving the question of whether it was a congenital mal-development or a growth arising later in life at present unanswered.

Before concluding it may be of interest to note the relationship of the symptoms during life to the findings at autopsy. It is evident that during the early development of the growth the patient had no difficulty in swallowing. This is remarkable, for, although it is probable that the growth had not at that time compressed the lumen to the extent it did later, yet it is surprising that with such an overgrowth of muscular tissue some incoordination of action should not have occurred. If one considers also the various directions of the muscular fibres

and the relative smallness of the longitudinal coat, this absence of early dysphagia becomes even more surprising.   Whether the symptoms at their first onset were due to actual narrowing of the lumen or to muscular incoordination it is impossible to say, but the fact that they disappeared for over a year makes the latter more probable.   This temporary disappearance of symptoms is characteristic of the common form of muscular incoordination of the oesophagus which Hertz (22) describes as achalasia.   Probably towards the end the chief obstruction was mechanical, due to the compression of the lumen by the upper swelling.

In conclusion I desire to express my sincere thanks to many colleagues who have furnished information about this case or about specimens of oesophageal growths in their possession.   I must especially thank Miss Eaves, of Sheffield University, for preparing microscopical sections, Professor Douglas for his valuable help as to the histology, and Drs. Knox and Watson for permission to reproduce their excellent radiograms.   Fig. 3, Plate 31, is reproduced by kind permission of Messrs. Longmans, Green & Co.

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DESCRIPTION OF FIGURES.

PLATE 24.   Oesophagus, anterior surface.

PLATE 25.   Oesophagus, laid open to show lumen.

PLATE 26.   Radiogram of thorax, taken March 1913, by Dr. E. Watson, Dublin.

PLATES 27, 28, 29, 30.   Radiograms of thorax, before and after bismuth meal, taken December 1914, by Dr. Knox, London.

PLATE 31, FIG. 1.   Section through upper oesophagus.   (× 10.)
FIG. 2.   Ditto.   Microphotograph.   (× 8.)
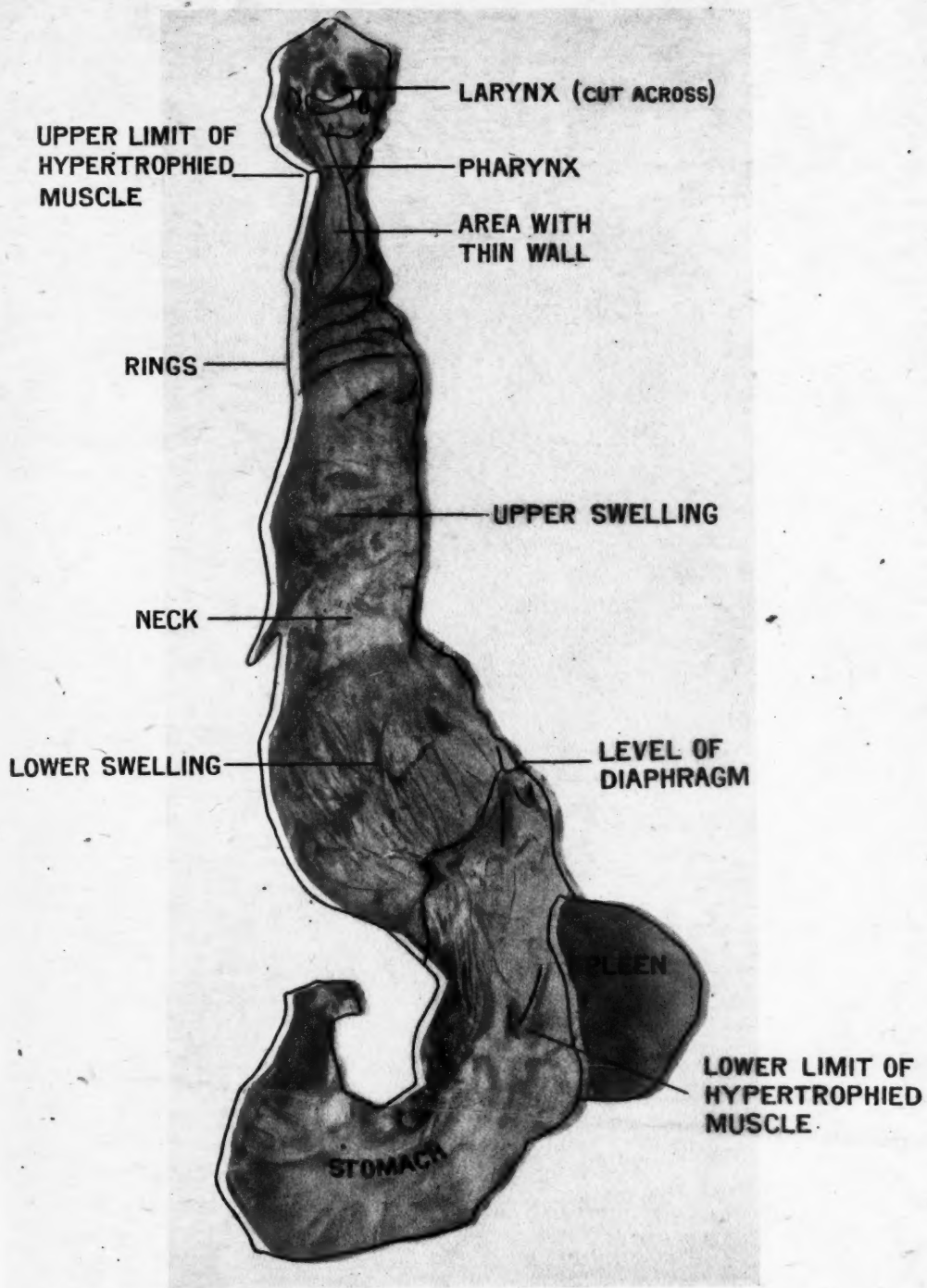FIG. 3.   Section of normal oesophagus.

PLATE 32, FIG. 1.   Section through cardiac stomach, in region of fibromyomatous growth. Microphotograph.   (× 8 diam.)
FIG. 2.   Ditto, just below region of growth.   Microphotograph.   (× 8 diam.)

LARYNX (CUT ACROSS)

UPPER LIMIT OF HYPERTROPHIED MUSCLE

PHARYNX

AREA WITH THIN WALL

RINGS

UPPER SWELLING

NECK

LOWER SWELLING

LEVEL OF DIAPHRAGM

SPLEEN

LOWER LIMIT OF HYPERTROPHIED MUSCLE

STOMACH
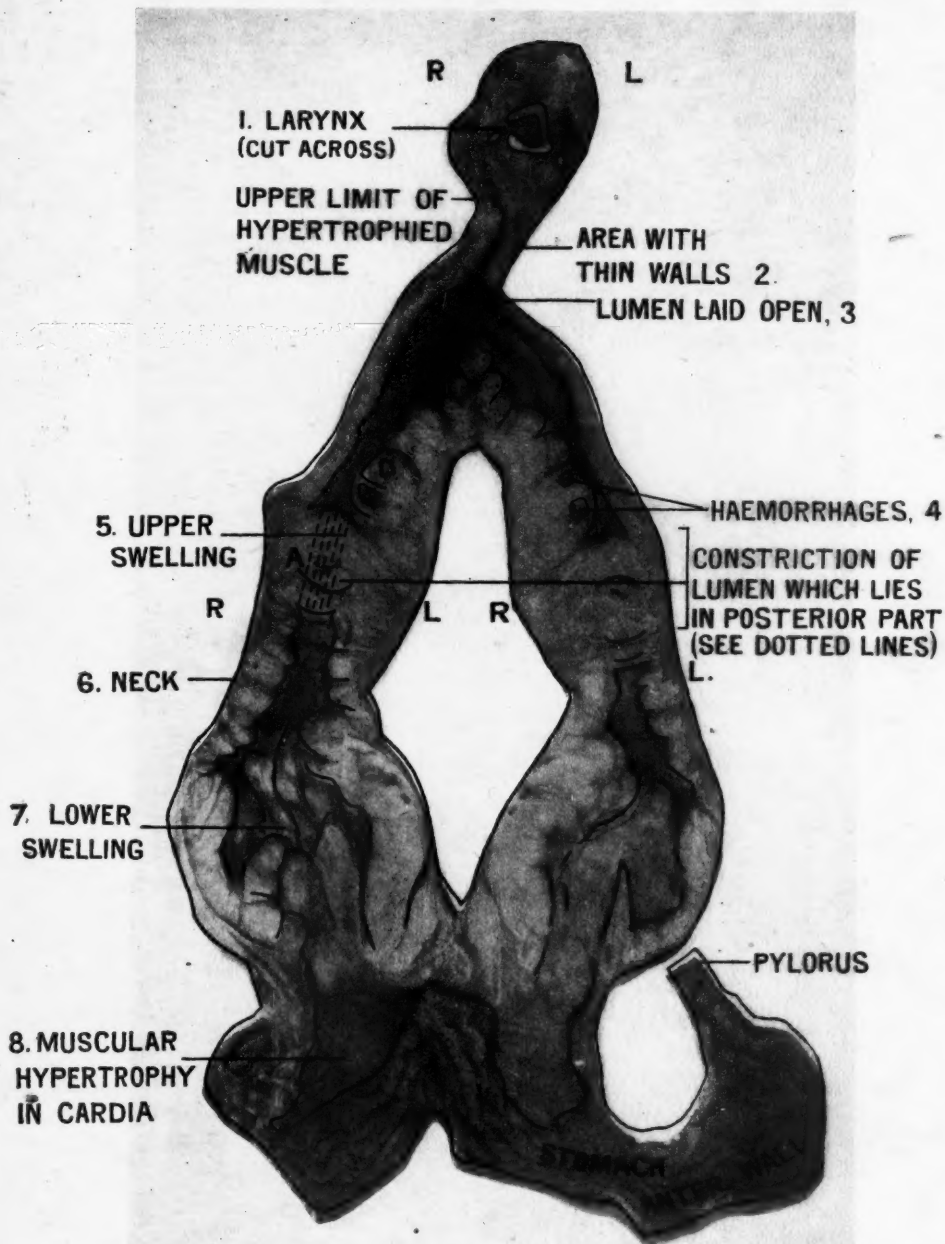
THE OESOPHAGUS HAS BEEN LAID OPEN BY A VERTICAL TRANSVERSE
INCISION. AND THE ANTERIOR PORTION TURNED OVER TO THE RIGHT.
THE INCISION STOPS AT THE UPPER PART OF THE TUBE.

RADIOGRAM TAKEN MARCH 1913
BY DR E. W. H. DUBLIN
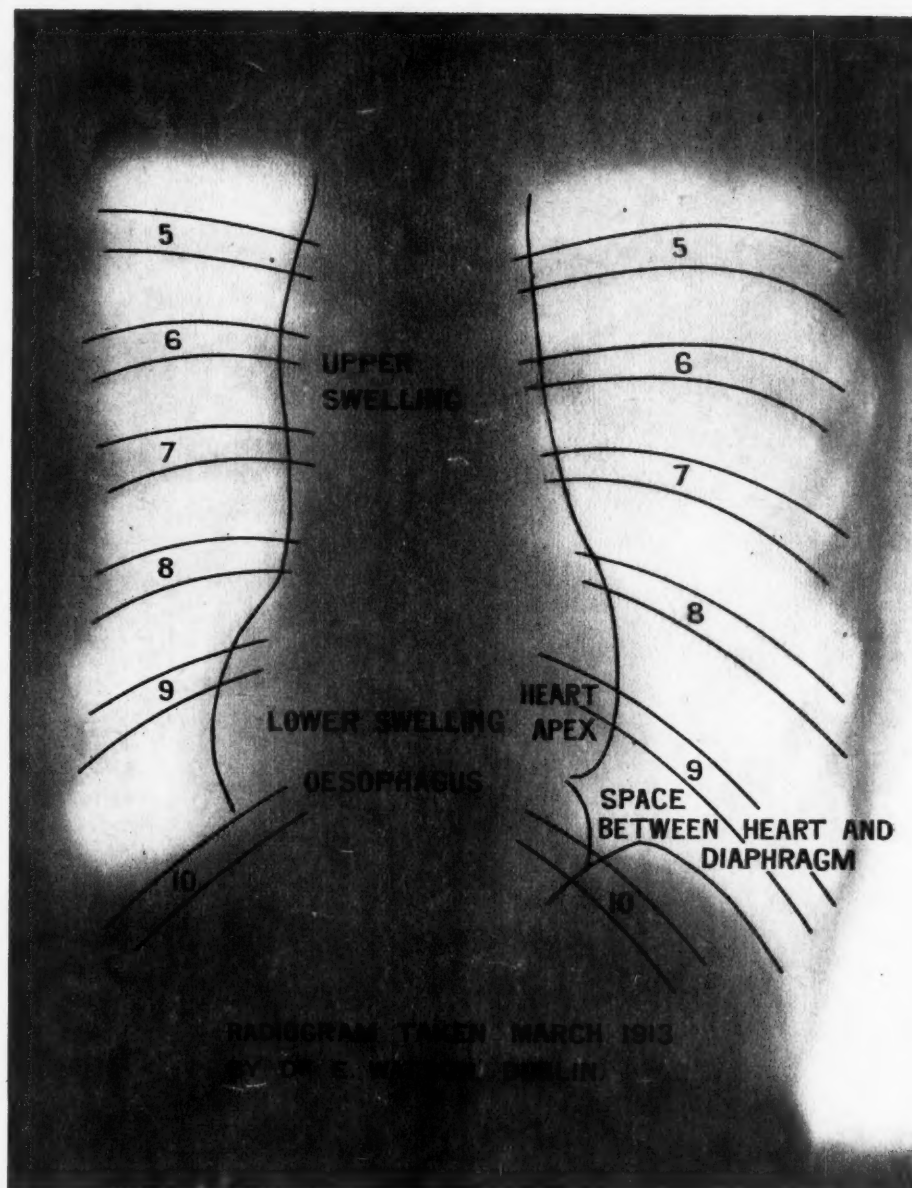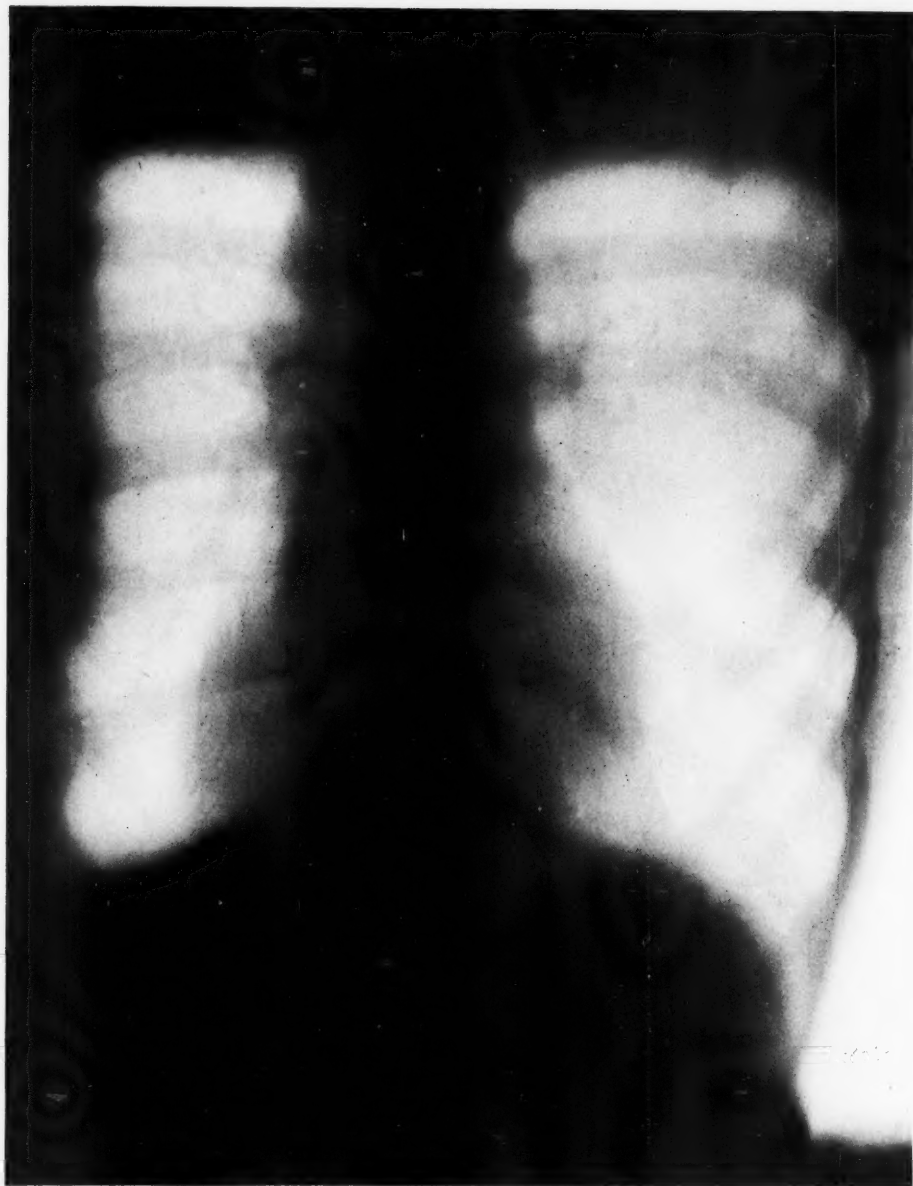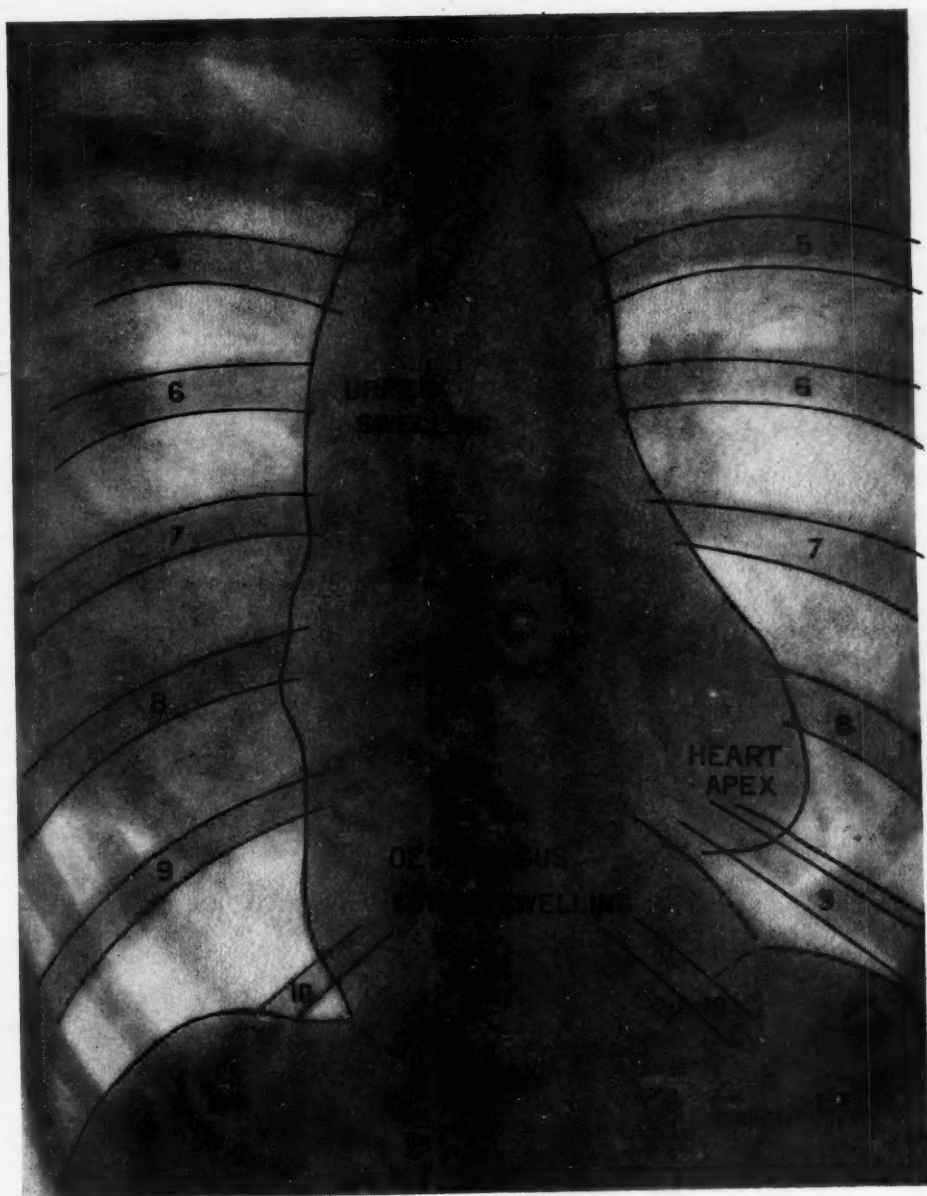
RADIOGRAM TAKEN DECEMBER 1914 BY
DR. KNOX, LONDON, PREVIOUS TO BISMUTH MEAL.
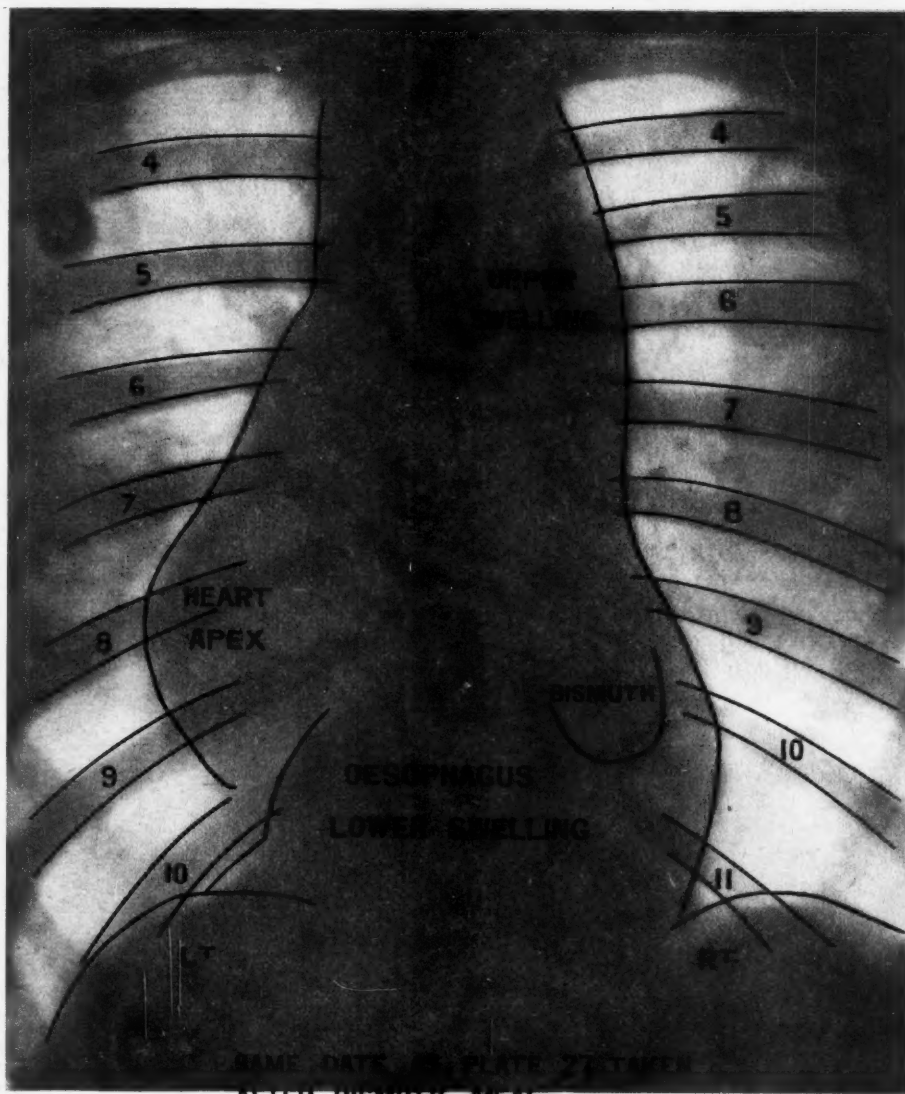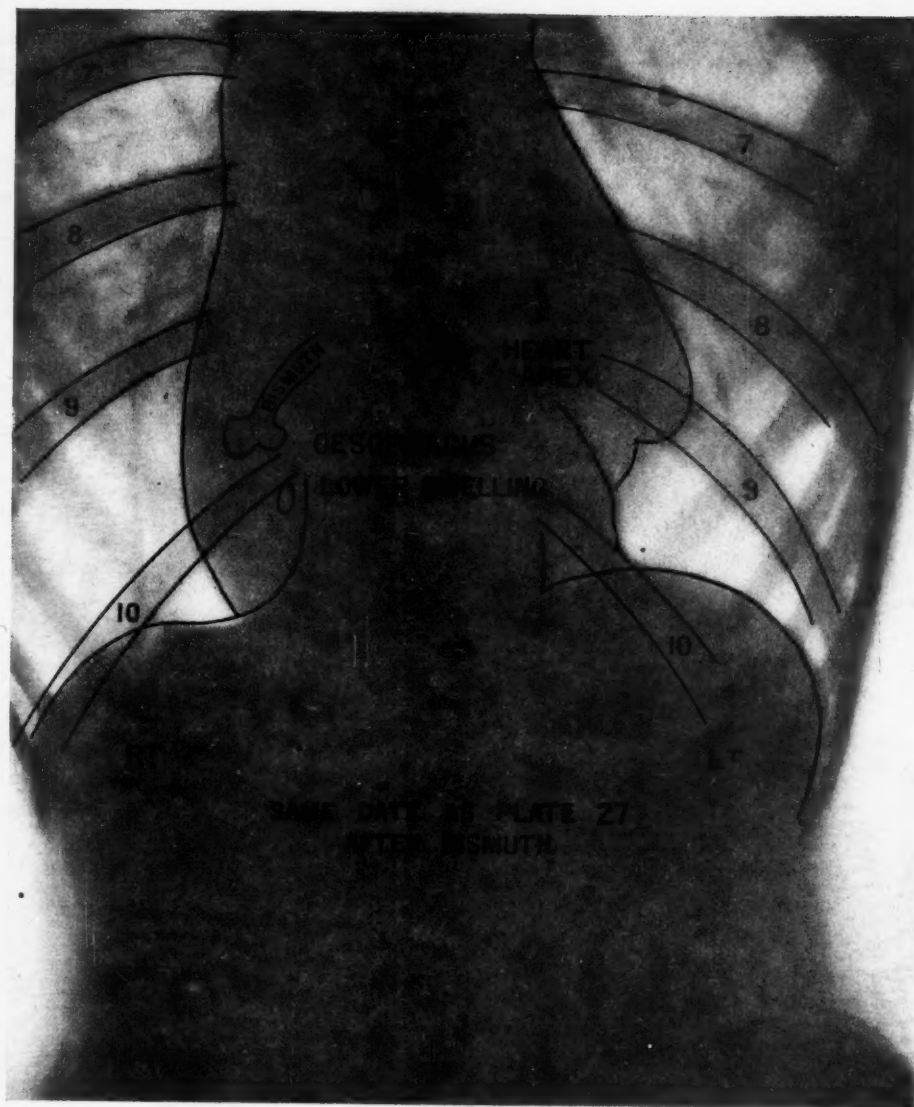
AFTER BISMUTH MEAL.

SAME DATE AS PLATE 27
AFTER BISMUTH.
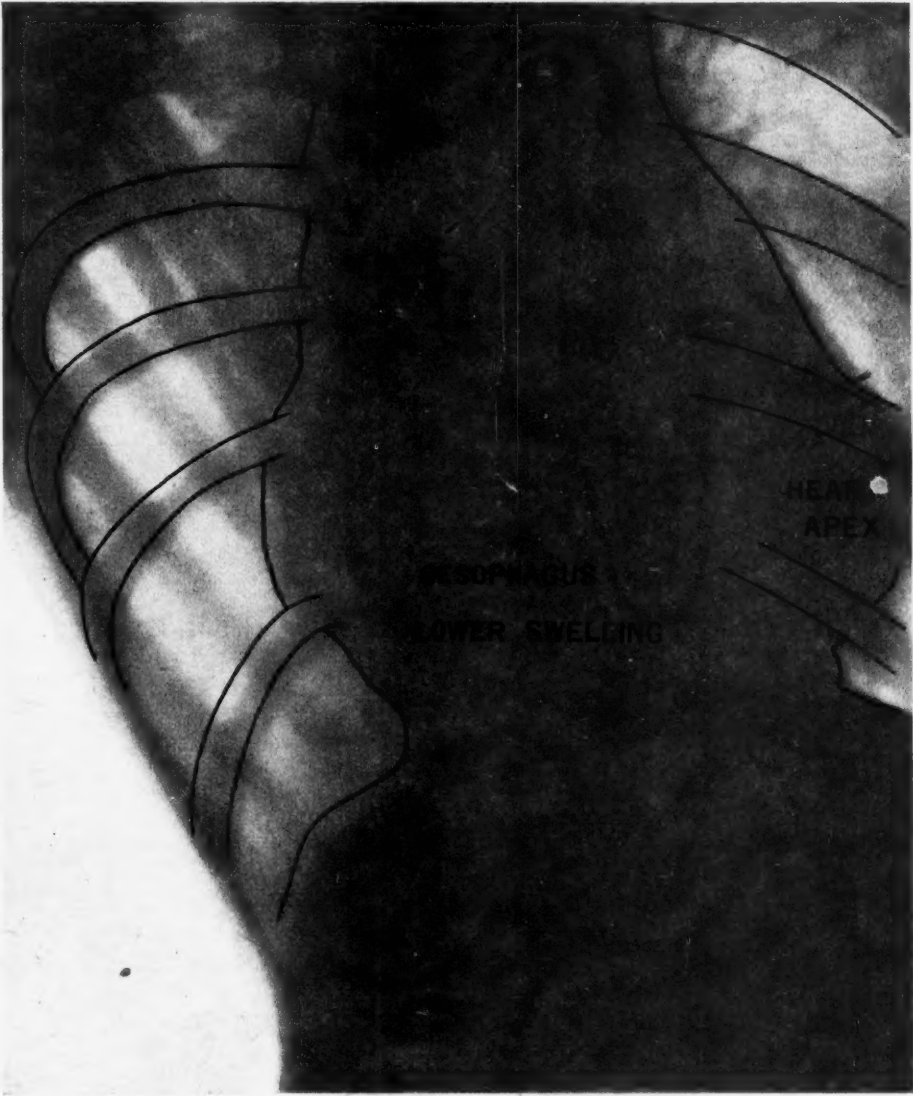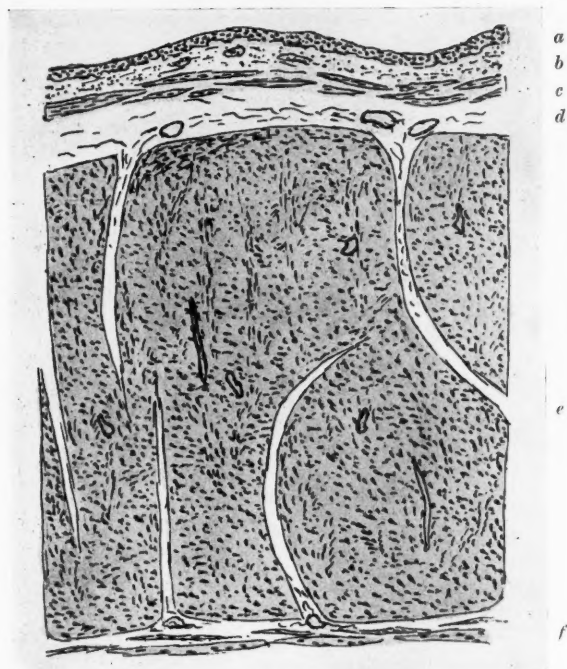
FIG. 1. Oesophagus: transverse section of lateral wall at 7 cm. below cricoid. *a*, epithelium; *b*, mucosa; *c*, muscularis mucosae; *d*, submucosa; *e*, hypertrophied circular muscle; *f*, longitudinal muscle. (× 10.)
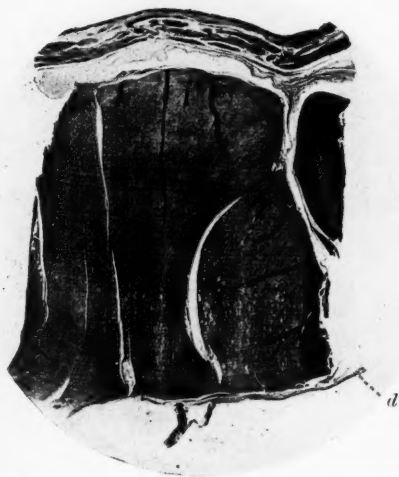
FIG. 2. Section of oesophagus from upper swelling. *a*, mucosa; *b*, submucosa; *c*, circular muscular coat; *d*, longitudinal muscular coat. (× 8 diam.)
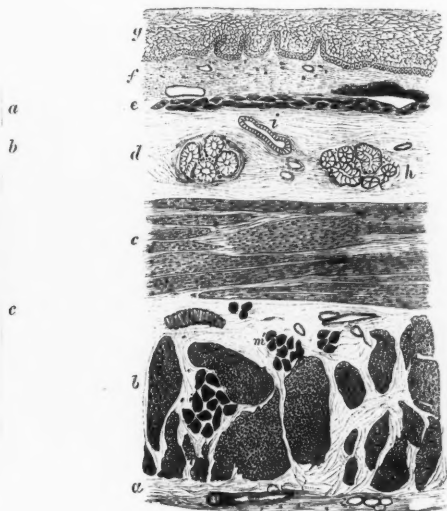
FIG. 3. Normal oesophagus. *a*, external coat; *b*, longitudinal muscle; *c*, circular muscle; *d*, submucosa; *e*, muscularis mucosae; *f*, mucosa; *g*, epithelium.

Reproduced by permission of Messrs. Longmans, Green & Co., from Quain's *Anatomy*, vol. iii, part iv, Fig. 83.
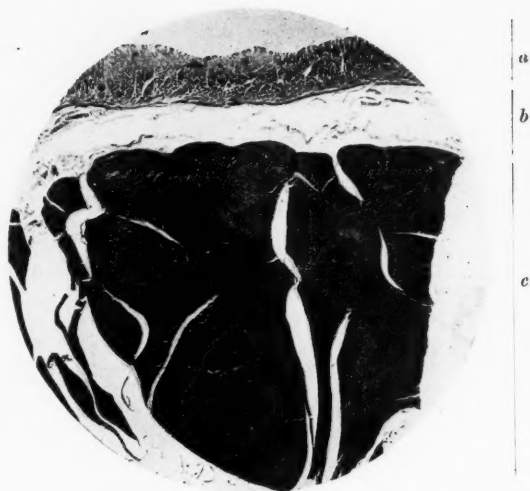
FIG. 1.   Section of cardiac stomach in region of fibromyomatous growth.
a, mucosa ; *b*, submucosa; *c*, muscularis.   (× 8 diam.)

FIG. 2.   Section of cardiac stomach just below region of growth.
a, mucosa; *b*, submucosa; *c*, muscularis. (× 8 diam.)   Note difference
of thickness of muscularis in the two sections and absence of folding
of mucosa in Fig. 1.

ON TRENCH FEVER AND ITS ALLIES

By W. P. HERRINGHAM

THOSE experienced in war tell me that it is always accompanied by many cases of slight fever which cannot be assigned to any of the diseases whose pathology is known. This has certainly been the case to a very large extent in this campaign.

During the winter of 1914–15 there was a great number of cases of pain and stiffness in the muscles which were diagnosed for the most part as 'myalgia', and there was also a certain number in which the sudden onset of fever and malaise with bronchitis led to the diagnosis of influenza. In one or two cases the *B. influenzae* was recovered from the sputum. The investigation was only made, so far as I know, in a few cases at a hospital where a mobile laboratory was quartered.

But about the end of April cases of short fever began to occur which appeared to most medical officers to be a new form of disease. The numbers affected were very great. It is impossible to give the total, for they were sent in under many headings. Myalgia and influenza were still retained, but pyrexia of unknown origin was the favourite diagnosis, and some were even called rheumatic fever. It was, however, one of the surprises of the campaign that rheumatic fever was hardly ever seen at that time. I do not think I saw more than five cases from October, 1914, to October, 1915. In the next six months, however, it was not uncommon.

These cases of short fever, which have occurred literally by the thousand, diminished to some extent in the autumn and winter of 1915–16, but increased again in the spring of 1916.

In the spring of 1915 medical officers were specially struck by the relapsing nature of the illness. It was chiefly this which led them to believe that they were dealing with a new complaint. The excellent clinical description given by J. H. P. Graham in the *Lancet* of September 25, 1915, and the longer paper by H. C. Rankin and G. H. Hunt (*Lancet*, November 20, 1915), describe the disease as they saw it. In the *British Medical Journal* of February 12, 1916, J. W. McNee and A. Renshaw gave a large number of typical charts and an elaborate account of the experiments and clinical observations they had made in order to determine its pathology. This relapsing form became known as 'Trench Fever', and was even allowed officially under the form of P. U. O. Trench Fever.

It occurred equally among men and officers, but it was at first seen only among two classes—those who had been at the front, whether in trenches, gun positions, or similar duties, and those attached, whether as officers, sisters, or orderlies, to field ambulances and clearing stations to which the patients were conveyed. I was regularly visiting the hospital which was at ——. There were 2,000 troops there, but I did not see trench fever cases at that hospital till late in December, 1915. I find that on Christmas Day I noted two cases, whose charts are so characteristic that I reproduce them (Figs. 1 and 2). They were both men who had come down from the front to go through the schools of gunnery. Within a day or two a third man was admitted who was on duty at those schools and had never been at the front. It seems practically certain that he had caught the disease from the men who had come down, and there must have been numerous cases from those schools since that date.

It is to be noticed that nephritis, which is also frequent, though not nearly so common as these fevers, differs from them in two remarkable points. It is very rare, though not unknown, in officers, and it attacks men at the front, on the lines of communication, and at the base in about equal proportion. Whereas the name 'trench fever' has a justification in that the disease appears really to be connected with the conditions at the front, there is no reason whatever for using the term 'trench nephritis'.

The peculiar course of fever reproduced p. 431 is so unlike any ordinary illness that it impressed itself on the mind of medical officers. But there have always been seen along with it cases of fever which, though lasting about the same time, that is as a rule about ten days, have run a different course. In these the fever rises gradually to about the fifth day and then falls gradually to normal, the evening temperature being usually one or two degrees higher than that of the morning. If the one may be called the saddle-backed, the other may be called the hog-backed type of chart. Rankin and Hunt gave an example in their Chart 3, and Fig. 3 is a somewhat similar chart. A bacteriologist, who was attempting to discover whether the poison of trench fever was conveyed by lice, allowed several lice from fever cases to bite him on the forearm for four days in succession. He was attacked by a severe fever of the hog-backed type. But the experiment, though suggestive, was inconclusive, because the lice were not all from one patient, and the patients from whom they were taken were not followed up. In McNee's experiments, again, the fever produced by inoculation did not always reproduce the relapsing form of the original case. The symptoms of the hog-backed type of fever are not different from those of the saddle-backed or relapsing form, but these are themselves, with the exception of the shin pains, so like the general malaise found in all fevers, that their occurrence can hardly be said to prove a common infection for the two types.

Before, however, discussing these symptoms I will state the results of an inquiry into the cases which occurred in one Division whose A.D.M.C. asked me if I would assist him in discovering the cause. Three Divisions, A, B, and C, lay

in that order next one another.   All occupied low ground and were exposed to
the same conditions.   It is not advisable to give the actual number of cases in
each, but taking 'x' to represent a certain unit, and taking the nearest multiple
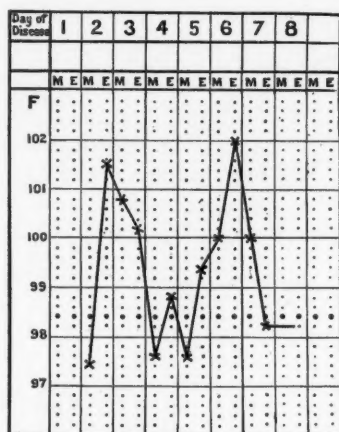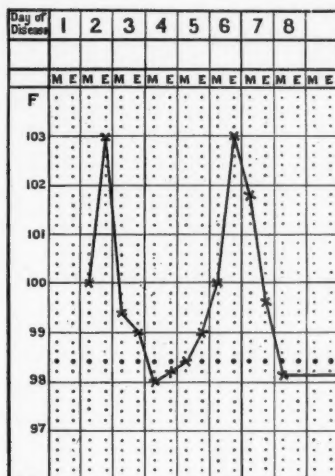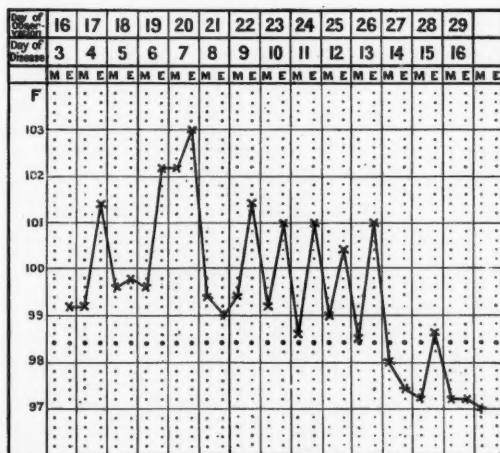

FIG. 1.

FIG. 2.

FIG. 3.

of 'x' when the real number is not actually divisible by 'x', the number of
cases under the headings 'influenza' or 'P.U.O.' in each Division for the various
weeks is as follows:

| Week ending	Division 'A'.	Week ending	Division 'B'.	Week ending	Division 'C'.
May 7	4 x				
,, 14	2 x				
,, 21	0				
,, 28	2 x				
June 4	3 x				
,, 11	12 x				
,, 18	10 x				
,, 25	9 x				
July 2	20 x				
,, 9	18 x	July 11	2 x		
,, 16	11 x	,, 18	3 x	July 17	8 x
,, 23	14 x	,, 25	5 x	,, 24	18 x
,, 30	15 x	Aug. 1	5 x	,, 31	29 x
Aug. 6	13 x	,, 8	7 x	Aug. 1 and 2	8 x
,, 13	17 x	,, 22	2 x	,, 9	20 x
,, 20	13 x	,, 29	2 x	,, 17	15 x
				,, 24	21 x
				,, 31	24 x

In Division B there were said to have been no cases until the second week in July. In Division C cases appeared in June, but did not begin to be numerous until July.

There is thus a remarkable difference between the Divisions. The centre Division suffered very little, while those on either side had very many cases. In Division A the distribution of cases was very unequal among the different battalions. There was no possibility of distinguishing them by the positions they occupied, since each was continually shifting ground and occupying billets or trenches that had been occupied by others. I inquired, however, also into the personal cleanliness of each, as I had in my mind the possibility of infection through lice.

Battalion	(i) had a total of	10 x.	It was very clean.
,,	(ii)	,, 15 x	dirty.
,,	(iii)	,, 2 x	excellent.
,,	(iv)	,, 13 x	fair.
,,	(v)	,, 12 x	clean.
,,	(vi)	,, 6 x	clean.
,,	(vii)	,, 4 x	moderate.
,,	(viii)	,, 2 x	moderate.
,,	(ix)	,, 26 x	very dirty.
,,	(x)	,, 9 x	clean.
,,	(xi)	,, 6 x	very clean.
,,	(xii)	,, 7 x	rather dirty.
,,	(xiii)	,, 12 x	clean.
,,	(xiv)	,, 8 x	clean.
,,	(xv)	,, 7 x	clean.
,,	(xvi)	,, 4 x	very dirty.
Bde. R.F.A.	(a)	,, 1 x	The only discoverable difference was that (c) occupied swampy ground, while the others were on rising ground.
,,	(b)	,, 1 x	
,,	(c)	,, 7 x	
,,	(d)	,, 0	

The M.O. of one battalion which was severely affected sent me an elaborate chart showing the incidence of the disease and the positions occupied by the battalion. He was killed shortly afterwards.

The chart shows that locality, whether in the trenches or in billets, had no effect on the incidence of cases. The same conclusion was drawn from the
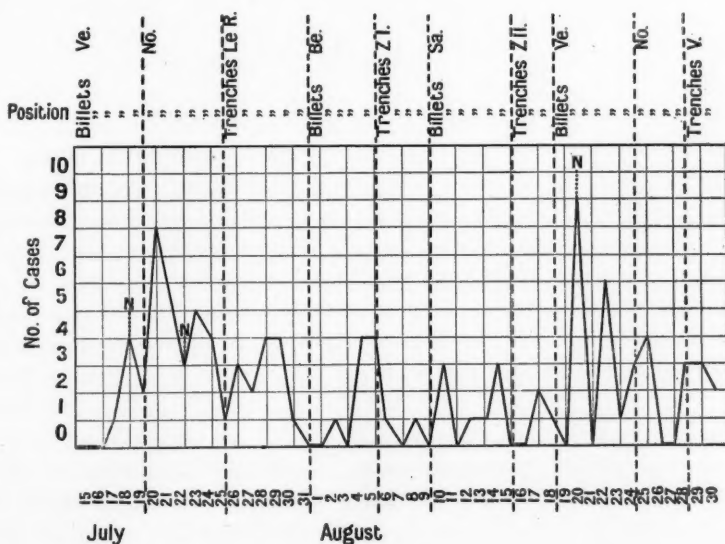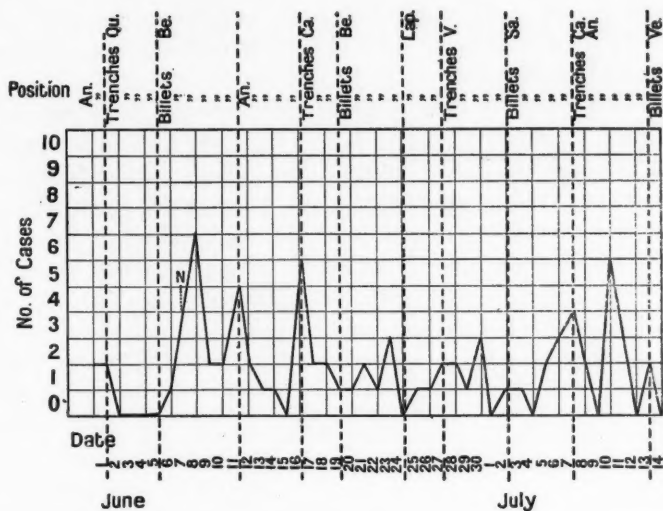
incidence of cases in the three Divisions, for there was nothing to choose between the areas occupied by them.

The two sources of infection which have been in the mind of all officers of the medical services are lice and some kind of fly or mosquito. There are difficulties in both hypotheses.

It has been sometimes stated that the continuance of the disease during the winter months is conclusive against flies or mosquitoes. I do not think this is true, for I have seen mosquitoes throughout the winter. But it is impossible to explain how one Division, lying between two others which were badly affected, in ground quite as full of mosquitoes as theirs, should escape so much more lightly if these insects conveyed the disease. The statements of patients are valueless. Most men do not notice bites, and all were bitten by so many insects that they could not tell one from another.

On the other hand, many officers and sisters working in clearing stations have had the fever. None of them can have had more than an accidental louse-bite, and some of them have declared that they have never been bitten by lice at all. The D.A.D.M.S. of Division 'C' told me that in the summer, when the fever appeared, the men were not nearly so lousy as during the winter, and indeed were little troubled by lice. But it is noteworthy that Division 'B', which had but few cases, had much better facilities for baths than either of the other two, and that in Division 'A' the incidence is, on the whole, though with striking exceptions, greater on the dirty battalions than on those which were clean.

The question must be settled by experiment. The case of the medical officer mentioned above is, I believe, the only instance in which a fever was produced by the biting of lice, though the experiment was repeated several times.

The symptoms of these fevers vary in different cases and at different times, and are never much more than the common denominator of all fevers. The onset is sometimes gradual, by a few days of general discomfort or weakness, but more often sudden. It is common for a man to say that he actually fell down while on some duty, taken by what he calls faintness or giddiness, or weakness of the legs. I do not think, however, that I have seen so sudden an onset in the case of a hospital orderly. I expect, therefore, that in most cases the man was sick before he fell. The hospital orderly would be able to report sick more readily, and therefore would avoid carrying on his work to the point of sudden failure.

The fever was almost always fairly high when the man was first seen. It seldom rose above 103° F., and was usually about 102° F. If seen on the first day it was often lower than that. In the saddle-backed type it fell on the third, fourth, or even the fifth day, usually to a point below the normal, remained normal or sub-normal for a day or two, and then rose again sometimes higher than in the first bout, but more often not so high. Many had no such relapse and recovered after one bout of fever. Others, as recorded by McNee, had

several. Probably these cases were more numerous than we at the front knew, for such patients were transferred to the base in large numbers. The continuous or hog-backed type reached to about the same height of fever, but showed no definite relapse.

I am told by officers who have been in Malta that they speak there of a three-day, an eight-day, and a twelve-day fever which yet seem to be one disease, the three-day being a fever of one bout, the twelve-day a fever of two bouts, and the eight-day a continuous fever. If this is so, it provides an interesting analogy with the short fevers of Flanders.

The pulse is nearly always below 100, varying with the temperature. The various sites of pain, in the head and especially between the eyes, in the back, where it is sometimes very severe, in the left side and epigastrium, and in the legs, have been often described. The most characteristic, though not constant, is that in the lower limbs. Sometimes it is referred to the thighs, sometimes to the neighbourhood of the knees, though not to the joint itself, but the most striking and the commonest is that in the legs. Sometimes this is felt in the muscles of the calf, but usually it is in the shins. In some cases it prevents sleep. It is often accompanied by great tenderness, and I have seen men who could not bear the weight of the blankets on their legs. But it is a peculiar thing that these cases of tenderness seem to occur in groups or at certain times. Graham does not mention it, and Rankin and Hunt say that it was slight in their cases. Some have thought that they could detect a little thickening as if from periostitis, but I have never seen any. The pains sometimes occur only during the bouts of fever, but usually last during the remission, and sometimes they, as well as the tenderness in the shins, last long after the fever has subsided. In some cases the patient could tell by a sensation of malaise that the fever was going to recur. But others, as mentioned by Hunt, did not know that they were feverish, even when the temperature was quite high.

Catarrh is usually absent, but in one field ambulance it was reported as common; it was probably a local accident. Nausea and vomiting were noted by Graham, but are, so far as I have seen, exceptional. Constipation is the rule. Diarrhoea is hardly ever present.

Rankin and Hunt found that when the fever was past their patients quickly became quite well. But Graham noticed great exhaustion after some attacks. There is no doubt that a good many of the cases take a long time to recover, and many medical officers have spoken to me of tachycardia on slight exertion as a common sequel. Considering, however, the large number of cases we have had, this occurs in only a small proportion of the total.

Graham, Rankin, and Hunt saw no bronchitis in the cases they treated during the summer, but during the winter bronchitis was very common in the army; as might be expected, these patients were not exempt.

I have not seen or heard of any case in which there was endocarditis or enlargement of the spleen. The latter symptom indeed would always lead to the provisional diagnosis of an enteric fever. There is never any considerable

or permanent albuminuria, and in the great majority of cases there is none at all, but in a few cases a trace has been found, which has soon disappeared. No case has proved fatal, and the great majority of the patients have recovered in a fortnight.

These fevers were at first thought to be some kind of enteric. It was not until hundreds of cases had been examined in the laboratories up and down the line that we could accept it as certain that there was a short fever which was not an enteric. The most difficult suggestion to disprove is that these fevers are an enteric modified by inoculation. Seeing however that neither can enteric organisms be grown from blood, stools, or urine, nor do the agglutinative changes of enteric appear in the blood, it is proper rather to ask on what ground such a suggestion is made. There really is no reason at all that supports it. It is in addition highly improbable that there should be such a large number of modified enteric cases, when there are so few that are regular.

Much more difficult is it to exclude influenza. It is true that catarrhal symptoms are rare, and that our original notion of influenza is that of a catarrhal fever. It is true that the B. influenzae has been repeatedly sought and never found. But the real truth is that the term 'influenza' is to us what a 'placebo' is to a patient, or 'that blessed word Mesopotamia' (which perhaps will lose its virtue now) to the religiously minded. When we diagnose a case as influenza, unless it is proved bacteriologically or occurs in an epidemic of which there is good bacteriological evidence, we mean that it is a 'pyrexia of unknown origin'. The curious relapses that mark one form of this fever are quite unlike anything that occurs in cases of influenza.

A great advance was made by McNee and Renshaw. In the first place, they were able to observe their cases for a longer time than the other medical officers, and to watch many relapses in regular succession. In the second place, they were able by inoculation with the blood of patients to produce fever in healthy men. And in the third they proved that the infecting body was connected with or included in the red corpuscles, and was not in the serum of the blood. They failed to find any micro-organisms which would account for the disease.

The treatment of these fevers has been uniformly without effect unless that in some cases morphia has relieved pain. Salicylate of soda and aspirin have been tried everywhere, for these drugs are in modern opinion the panacea for all diseases. They are still used, though experience has shown them to be useless. Quinine, potassium iodide, mercury, belladonna, and arsenic have given no better results. In a short series of cases Hunt used salvarsan, but it had no effect. In some cases we have given small doses of opium regularly. Not one of these methods has modified the course of the fever. In cases of severe pain morphia has sometimes, though by no means always, enabled a man to sleep.

ON THE CASES OF CEREBRO-SPINAL FEVER TREATED AT THE ISOLATION CAMP CASUALTY CLEARING STATION

By ALEXANDER PRESSLIE and W. E. LINDSAY

SINCE October, 1915, to present date, May 9, the total number of true cases have been thirty-nine, diagnosis in each case being verified by bacteriological examinations. Fatal cases were fifteen. Cases recovered and sent to base, sixteen. Number present in camp, eight. Four of these are definitely convalescent and are marked for evacuation. Remaining four are still acutely ill, two of them seriously. The death-rate is 38 per cent. of the total cases. One of us has attended thirty-five out of the thirty-nine. Cases are never evacuated to the base until they are firmly advanced in convalescence and usually have had their temperature normal for several weeks. Of the fifteen fatal cases the bulk were of the so-called fulminating type and were hopeless from their admission, many of them dying within 24 hours to 48 hours after entering hospital, one recent case in $6\frac{1}{2}$ hours' time. Two cases, after apparently progressing towards recovery, gradually became hydrocephalic and died from inanition. Of the twenty cases which have definitely recovered to date sixteen were of a severe type, the remaining four being of a comparatively mild nature. In nineteen of these cases, after recovery there was apparently no permanent physical or mental impairment. In the remaining case the patient was stone deaf. In all cases the duration of illness before admission here varied from a few days up to a fortnight or even longer.

The long duration did not necessarily render the case hopeless, although it is obviously very important to see the cases as early as possible. One case, for example, admitted February 18, 1916, had a history of twelve days' duration of illness. This case was unconscious, with well-marked subsultus tendinum and high delirium, for a week after admission here. He eventually recovered and was evacuated to the base on March 17, 1916. A tolerably common duration previous to admission here has been a week.

We do not think the appearance of the cerebro-spinal fluid can give any criterion as to the severity of the case or otherwise. Some cases with thick pus-laden fluids have proved comparatively easy to cure, and again cases with fluid showing a small amount of turbidity showed the reverse.

We have found that early high delirium is not a good sign, and a temperature

with only small variations between the morning and evening readings is like-wise rather unfavourable, but cases with a big swing, say of a few degrees, invariably did well.

Treatment. Daily lumbar puncturing, emptying the spinal canal on each occasion *as much as possible.* We have used this as the routine treatment and continue until all pressure symptoms are gone, such as headaches, and even then, if the temperature is still above normal, continue it until the temperature has been normal for at least four successive days. We always withdraw fluid until it is below the normal pressure, and have seen no bad results, either temporary or permanent, from this. With very few exceptions the patients had a general anaesthetic, chloroform being usually employed. We have found that more fluid can be withdrawn under a general anaesthetic than if nothing was given. The daily dose of chloroform seems to do no harm, for the common rule is to give them chloroform ten or twelve times in successive days on an average, and no bad effects have followed.

At first we used Mulford's, Burroughs Wellcome's, and Parke Davies's serums, but gave them up as we became quite convinced that they do no good, and for a long time treated the cases with simple lumbar puncture. Latterly, we have used the Lister Institute serum made for the War Office, but we cannot say that the results are any better than with simple lumbar puncture.

In February we had ten cases. Eight of them recovered and were sent to the base; two died, making a death-rate of 20 per cent. In April we had also ten cases. One case recovered and was sent to the base; four are convalescent and are now awaiting evacuation; three have died; two cases are still seriously ill. The death-rate is then 30 per cent. up to the present (see later note). The February cases had no serum given. The April ones all had serum.

We think that after four daily injections of 30 c.c. of serum it should be discontinued and simple lumbar puncture only done, but it appears to us that this serum no more than the other serums seems to meet the strain of the present epidemic in France. At any rate we have got no better result since using it. It has not modified the symptoms or cut short the duration of the disease. In fact after simple lumbar puncture the patients are more comfortable than when the serum is introduced, which is obvious seeing that by the injection the intrathecal pressure is restored, at any rate to some extent.

For severe pains in any part of the body we have used hypodermic injections of morphia pretty freely with quite good results. For persistent sleeplessness and delirium, common complications in cerebro-spinal fever, we have found a mixture of chloral and bromide quite satisfactory. For irregularity of the pulse and other signs of cardiac weakness, hypodermic injections of strychnine are very suitable. Also half-ounce doses of whisky every four hours have answered very well. When there has been incontinence of urine we have been able to stop it in some cases by using the catheter every three hours or thereabouts thus reducing the risk of bed-sores besides increasing the comfort of the patient.

We have used hexamine extensively in the most of our cases, the dosage being high, 20 grains every four hours, that is, 120 grains in twenty-four hours, and continued it for weeks, in one case for six weeks.

In December and January last we took the cerebro-spinal fluid from one patient who had been having hexamine for four days with a lumbar puncture each day and had the fluid examined for free formaldehyde. The report stated that it was present in the proportion of 22·5 in 100,000 parts. We kept the same patient for seven days on hexamine without lumbar puncturing and at the end of the week collected the fluid, lumbar puncturing only at the end of the seven days, had it examined and found that free formaldehyde was present to the extent of 45 parts in 100,000. We have continued this treatment in the bulk of the cases, as it is obviously of value to have such a powerful bactericide present in the spinal canal. In no case has the hexamine produced any bad effects. One or two of the cases showed haematuria and it was stopped for a time, but as haematuria is a fairly common complication in cerebro-spinal fever and as some cases showed it before they were put on to hexamine it was probably a coincidence.

Dieting has been liberal in quantity and quality. If at all possible, patients, even those with a fairly high temperature, are kept on a solid diet of porridge, fish, chicken, fresh vegetables, eggs, milk pudding, tinned fruit, and so on. We have always emphasized to the nursing staff the importance of plenty of food. The following is what we have been giving to cerebro-spinal fever patients :

7.30 a.m.	10.30 a.m.	12.30 p.m.	3.30 p.m.
Porridge, tea, bread and butter	Soup or cocoa and bread	Tinned chicken or fish, potatoes, milk pudding, fruit (bottled or stewed), bread	2 eggs, tea, bread and jam, cake, fresh fruit

7.0 p.m.		
Fresh chicken or fish and soup. Bread and butter		Through the night milk is given frequently

In addition convalescing patients are given 10 ounces of stout per diem.

We have kept the bowels freely evacuated, and if a day passed without a motion laxative medicine was given the same evening. The comfort of these patients has been specially studied. We put them all on beds, with frequent changes of body and bed linen. As soon as they are fit, books and periodicals are provided, and if at all possible we have allowed them cigarettes and in certain cases a pipe and tobacco. We have insisted on one orderly at least being always present in each ward night and day, and we have used every endeavour to keep the patients ignorant of the true nature of the disease, our intention being to keep the patients' attention away from their disease as much as possible.

Cerebro-spinal fever cases require a good deal of attention, and good nursing orderlies, preferably with experience of the disease, are indispensable.

The points we consider important are :

1. Early diagnosis with consequent early start of treatment.

Summary of Bacteriological Findings in Cases of Cerebro-spinal Fever occurring in a Casualty Clearing Station
23/x/15 to 7/v/16.

Date of Admission.	No.	Type of Case.	Result.	Date of Evacuation or Death.	Appearance of Fluid.	Chemical Tests.		Bacteriological.		Cells present.		
						Albumin.	Fehling's Test.	Microscopl.	Culture.	Polys.	Monos.	Other Cells.
1915												
23/x	1	severe	recovered	10/xii/15	purulent	+ +	—	+ + +		excess		
7/xi	2	severe	death	11/xi/15	purulent	+	—	+		excess		
12/xi	3	chronic	death	9/i/16	turbid	+	—	+ +	+	excess		
19/xi	4	severe	recovered	4/i/16	purulent	+ +	—	+	+	excess		
4/xii	5	fulmt.	death	5/xii/15	purulent	+ + +	—	+ +		excess		
10/xii	6	fulmt.	death	11/xii/15	purulent	+ + +	—	+ +		excess		
12/xii	7	fulmt.	death	14/xii/15	purulent	+	—	+ +		excess		
15/xii	8	chronic	recovered	7/ii/16	turbid	+	—	—	+	excess		
18/xii	9	severe	recovered	7/ii/16	turbid	+ +	—	+		excess		
19/xii	10	severe	recovered	7/ii/16	purulent	+	—	+ +	—	excess		
22/xii	11	fulmt.	death	24/xii/15	turbid	+	—	+		excess		
1916												
1/i	12	severe	death	15/i/16	purulent	+ +	—	+ +	+ +	excess		
14/i	13	severe	death	18/i/16	purulent	+	—	+	+	excess		
31/i	14	severe	death	12/ii/16	purulent	+ + +	—	—		excess		
6/ii	15	light	recovered	10/iii/16	sl. turbid	?	+	+		equal numbers Polys. and Monos.		
6/ii	16	severe	recovered	10/iii/16	turbid	+	—	+ +	+	excess		
7/ii	17	severe	recovered	17/iii/16	turbid	+	—	+	+ +	excess		
5/ii	18	light	recovered	10/iii/16	turbid	+ +	—	+ + +		excess		
7/ii	19	fulmt.	death	9/ii/16	turbid	+	—	+ +		excess		
18/ii	20	severe	recovered	17/iii/16	sl. turbid	+ +	—	+ +		88 %	6 %	6 %
21/ii	21	severe	recovered	10/iii/16	purulent	+ + +	—	+ + +	+ + +	excess		
20/ii	22	severe	recovered	17/iii/16	purulent	+ + +	—	+		83 %	11 %	6 %
23/ii	23	chronic	death	26/iv/16	purulent	+	—	+ + +		75 %	15 %	10 %
26/ii	24	severe	recovered	17/iii/16	sl. turbid	+ +	—	+		excess		
5/iii	25	fulmt.	death	8/iii/16	purulent	+ +	—	+ +		85 %	6 %	9 %
19/iii	26	light	recovered	2/v/16	purulent	+ +	—	+	+ +	65 %	12 %	23 %
27/iii	27	severe	recovered	2/v/16	turbid	+ +	—	+ + +	+ +	87 %	12 %	1 %
1/iv	28	severe	recovered	10/v/16	hazy	+	+	+	+ +	69 %	13 %	18 %
11/iv	29	severe	convalest.	20/iv/16	purulent	+ +	—	+		81 %	8 %	11 %
13/iv	30	severe	death	10/v/16	purulent	+ +	—	+ +	+	84 %	5 %	11 %
18/iv	31	light	convalest.	19/iv/16	sl. turbid	+ +	—	+ + +		78 %	11 %	11 %
19/iv	32	fulmt.	death	12/v/16	purulent	+ + +	—	+		excess		
20/iv	33	severe	convalest.	10/v/16	purulent	+ + +	—	+		excess		
21/v	34	severe	death	3/v/16	purulent	+ + +	—	+ +	+	excess		
22/iv	35	severe	convalest.	10/v/16	purulent	+	—	+ + +		excess		
23/iv	36	severe	convalest.	14/v/16	purulent	+ + +	—	+		excess		
28/iv	37	severe	convalest.		purulent	+	—	+ +		excess		
4/v	38	severe	death	11/v/16	purulent	+ + +	—	+ + +	+ +	excess	68 %	9 %	25 %
7/v	39	severe	death	15/v/16	purulent	+ + +	—	+		81 %	9 %	10 %
10/v	40	severe	convalest.		purulent		—	+		excess	Very degenerate	
12/v	41	severe	doubtful		purulent	+		+	+	80 %	5 %	6 %
15/v	42	severe			turbid							

{ Blood culture

2. Daily lumbar puncturing, removing as much fluid as possible on each occasion, until all pressure symptoms are gone, and the temperature has been normal for at least four successive days.

3. Good feeding, preferably solid, liberal in both quantity and quality.

4. Hexamine in large doses and continued over a long period if necessary.

5. Keeping the bowels freely evacuated.

6. Good nursing and constant attention to the needs of the patient.

7. Treating complications as they arise.

———————————

In continuance of above report two of the April cases have since died. The other five having recovered and been evacuated to the base, the death-rate for April is then 50 per cent. One other case, the last admitted before above report was written, has also died. It was of a severe type, showed no improvement, and death took place in less than four days after admission. Three other cases have been admitted to date, making total number of cases forty-two. One of these has died. This case on admission was maniacal and had at first to be forcibly held down in bed. He died five days after admission. For forty-eight hours before death there was a considerable amount of cardiac distress. In the remaining three cases in hospital at present the prognosis is quite good. One case is practically convalescent, another is greatly improved with temperature down, and the remaining case is progressing satisfactorily. The deaths out of the forty-two cases are thus nineteen, or 45 per cent. This is higher than in above report, but there have been a series of fulminating cases in the last few weeks, and as these appear to occur in cycles, there will probably be now a succession of a less severe type, tending to bring the percentage back to 39 per cent., which has been the average. An indication of this is that the last two cases, although not mild, were of a much less severe nature than the others for a month previous.

We may mention that one case, which was admitted last month, contracted German measles while here. He recovered and was sent to the base. This is the first case of cross-infection which has occurred here, although the hospital has occasionally been crowded.

FURTHER OBSERVATIONS ON 'TRENCH FEVER':

A RELAPSING FEVER OCCURRING WITH THE BRITISH TROOPS IN FRANCE

(A Report to the Medical Research Committee)

BY G. H. HUNT AND J. W. McNEE

THE disease now known to our armies as 'trench fever', which has been met with among the troops in France since the early summer of 1915, has in recent months been the subject of published investigations, in which both of us have taken part (Hunt and Rankin, *Lancet*, Nov. 20, 1915, and McNee, Renshaw, and Brunt, *British Medical Journal*, Feb. 12, 1916). Since these observations were published further work has been carried on, leading to results which we now propose to give. The points not hitherto discussed, or on which additional evidence has been collected, may be stated at once to show in what way the details now given amplify our previous experience and add to our knowledge of the disease as a whole.

These points are—

1. The duration of the disease, and its importance as a source of wastage in our armies.

2. Definite outbreaks of the disease in medical units.

3. Its means of transmission.

4. Its probable incubation period.

5. Attempts at specific treatment.

Symptomatology.

A brief account of the disease as it exhibits itself in the winter months will have some value, as in neither of the previous papers referred to was a very full account of the symptoms given. The following description, written by a patient himself, is so typical a picture of the illness as seen at present, that we cannot do better than quote it in full. This account was drawn up unaided, from notes the patient had kept in a diary.

'On Monday morning I felt ill. The general symptoms were a hot, drowsy, powerless feeling, accompanied by dull pains up the front of the legs. We had to go to the trenches at night, and on arrival I collapsed and slept in a dug-out all night. Tuesday morning I felt a lot better, and did not report sick, but on

Tuesday night pains began again, and on Wednesday I reported sick. I described the symptoms and had my temperature taken, which was high, and that night saw me in the hospital at A——, labelled "influenza". Thursday, Friday, and Saturday morning my temperature was normal though the pains were still there, and on Saturday afternoon I was sent to the hospital at S——. My temperature was taken there, which was 101 as far as I remember, and after describing the pains, &c., I was sent to bed labelled "trench fever". All day Sunday my temperature was still up, and the pains up the legs and in the head most violent. On Monday morning my pains got a lot better, and with it my temperature became normal and remained so all day Tuesday. On Wednesday morning my temperature rose again to 100, and at night was somewhere about 102, and the pains in my legs and head again became very bad. This continued all Thursday, and during the night my pains got much easier. On Friday my temperature was normal, and also on Saturday morning. On Tuesday (i.e. the next week) I was sent to this hospital at M——. My temperature remained normal and my pains very slight until the morning of the 23rd. During the afternoon of this day the pains in my legs and head again became very bad, and that night my temperature rose to 101, and remained high until the morning of the 26th, when it became normal and the pains decreased in violence. During the next three days the pains were much easier, and my temperature each night registered a little over 99. On the afternoon of the fourth day (29th) the pains became very bad and my temperature rose again to over 100 and remained so until the morning of the 2nd, when it became normal. During this attack my pains were more violent than in any of these attacks, and it was impossible to sleep. They stretched from the bottom of the legs right up the thighs, accompanied with a headache and a slight pain in the back. I may say that in the interval between my previous attacks the pains in the legs and head were always there, but to a much slighter degree. But after this (my fifth and last attack to date, in which the pains were more severe than any before), the pains completely died away and were not felt by me for about sixteen days, after which I felt them again slightly for three to four days, during which time my temperature registered a little over 99. Since which time (four days ago) I have not felt them, and my temperature has been normal. During the attacks I felt very weak and could hardly walk; I am now a lot stronger, but any undue exertion such as running, carrying anything, shows this weakness up.'

This description illustrates almost all the characteristic points, particularly the site of the pain, and the alleviation or complete disappearance of symptoms which accompany the fall of temperature. The onset with weakness and drowsiness is typical of one class of case, whereas in others sudden dizziness or a 'shivery feeling' usher in the disease. More rarely a feeling of *malaise* lasting a day or two precedes the attack. Certain symptoms, in view of our more numerous observations, may be referred to a little more in detail. Headache is invariable, usually frontal, and a very common complaint is of pain behind the eyes, increased by movement of them. Less commonly the headache is universal, and may be most intense in the nape of the neck: in two cases, indeed, pain and stiffness in this region were so intense that lumbar puncture was performed to exclude meningitis. Another important diagnostic point is the absence of any nasal or bronchial catarrh. The bowels are generally constipated during the pyrexia, and vomiting has sometimes occurred, possibly as a result of this. Diarrhoea is never seen, and its spontaneous occurrence would exclude a diagnosis of the disease.

When seen during a febrile period the patient looks flushed, but the eyes are clear and bright.   He frequently does not look as ill as the high fever would lead one to suspect, and various patients have been discovered reading at a table with temperature up to 104° F.   Less commonly the sense of weakness is much more profound, and the patient looks seriously ill.   Such cases have ome under grave suspicion of belonging to the enteric group, until the negative bacteriological examinations and the occurrence of typical short relapses proved them otherwise.

The tongue is often somewhat furred during the fever, but never becomes dry.   Routine examination of the heart, lungs, and abdomen has never revealed anything abnormal.   The spleen has not been found enlarged, although special attention has been paid to this point in some hundreds of cases.   Albuminuria, even in cases with very high fever, has never been observed.

Course of the Disease.

Two clinical varieties of the disease were distinguished in a previous paper (McNee and Renshaw), and named (1) the short type, (2) the long type.

The short type.   This type, when the disease first began to be recognized, was certainly much the predominant one, but this is no longer so.   In one account of the disease (Hunt and Rankin) thirty cases, mostly of this type, were described; in the other (McNee and Renshaw) all but twenty of the cases observed fell into this group.

The characteristic temperature chart shows a period of pyrexia lasting six to eight days.   In a number of cases there is an intermission, in which the temperature may come down to normal or almost normal, but without much, if any, relief from the symptoms.   Such an intermission, when it occurs, is met with between the third and fifth days, and is of short duration.   Coincident with the fall of the temperature to normal about the end of a week, all symptoms disappear at once, and the patient feels perfectly well.   A single relapse follows, usually after an interval of two to four days.   During the relapse all the previous symptoms return, but are never so severe as before.   This relapse marks the end of the illness, and the patient is generally fit for duty almost at once.   A number of such cases have been observed for weeks, and some even (R.A.M.C. personnel) over a period of months thereafter, without the least return of pain or fever, so that there can be no question (as has been suggested to us) of additional relapses occurring when the patient is not under observation, in this type of the disease.

The long type.   This type, from being one of comparative rarity, has now become during the winter months the commoner variety of the disease.   Here the illness takes on the character of a true relapsing fever, and as many as five or six relapses may be met with extending over a period of several weeks.   The symptomatology is identical with that of the previous type, the only distinction

being that the initial bout of fever is short (frequently about three days), and the relapses usually as severe as the original attack. No definite periodicity in the relapses can be traced from the examination of many charts.

Usually the first relapse occurs four or five days after the temperature has fallen to normal, but the intervals between subsequent relapses vary between three and thirteen days. During these intervals the temperature may remain normal, but more frequently it rises slightly above normal in the evenings.

After the last definite relapse, as indicated by a distinct spike on the temperature chart, has occurred, the patient is frequently by no means cured. Oscillations of temperature, with return of pains and headache, may recur over a period of weeks or (rarely) even months. During such recurrences the temperature is always found elevated, generally to about 99° F. or about 100° F. Such men are quite unfit to return to duty at once, and are practically all evacuated to the base, and many to England.

Duration of the Disease.

This is one of the most important considerations for armies in the field, where every source of wastage counts. We wish, therefore, to draw attention definitely to the fact that 'trench fever' as seen during the winter and spring months cannot be classed as a short disease. The longer, relapsing type prevails, and the average duration of a number of recent cases is certainly not less than *four to six weeks*, during which time and generally longer the man is unfit for active duty. This represents a period of loss but little short of that brought about by the milder cases of the enteric group and many wounds.

We have in addition charts which show relapses, or oscillations of temperature accompanied by definite symptoms, for a much longer period, in which the men remained unwell for nearly three months.

Thus the disease, which is now widespread among the troops in France, would seem, from the point of view of wastage alone, to merit every attention.

Outbreaks of the Disease in Medical Units.

Several such outbreaks have come more or less under our direct observation, and especially one at a casualty clearing station to which one of us was attached (G. H. H.). As such cases were so completely under control from the outset, they were studied with care, especially with regard to factors which might throw light on the means of infection, the incubation period, &c.

Between July 13, 1915, and January 2, 1916, thirteen men of the unit referred to above were affected with typical attacks of the disease. At first the cases developed with long intervals between them, i. e. between July 13 and October 5 four men fell sick at different times. During the second week of October two men fell ill, and in the months of November and December eleven

men (about one-tenth of the total strength) were admitted to hospital suffering from the disease. Both the short and the long type of cases occurred, and certain of the latter group must be referred to individually.

In investigating the outbreak special attention was paid to the following points :

1. Had the men affected been nursing patients suffering from the disease, or had they been in contact with other men in the unit who developed it ?

2. Had they been bitten by lice, or noticed them on their clothes ?

3. The point whether a man can have two separate attacks of the disease came up for consideration for reasons considered below.

(a) All but three (Ptes. C., Ch., and G.) had been attending cases of ' trench fever'. Pte. C. slept with Lance-Corporal T., and developed the disease six days after the latter fell ill. Pte. Ch. was never in the wards, nor did he sleep beside any of the men who fell ill. His duties were concerned with the cleaning of the hospital blankets, and the question at once arose as to whether he was infected by contact with the blankets, and if so, in what way. Pte. G. was a stretcher-bearer, and thus came into closer contact with the clothes and blankets of the patients admitted to hospital than with the patients themselves.

(b) Although every facility possible is given to men of the unit for bathing and changing their clothes, it is inevitable that their close contact with men from the trenches should lead to occasional infection with lice. Seven out of the thirteen men who fell ill stated that they had found lice from time to time on their clothes, and positive evidence on this matter is of greater value than a negative reply, since a few lice on the clothes may readily pass unnoticed unless a careful search for them is made.

(c) Three men (Sergt. M., Pte. N., and Pte. S.) were in hospital on two occasions, and the question whether they were suffering, on the second admission, from a new infection or a recurrence of the first, is of such importance both with regard to the duration of the disease and the question of immunity from fresh infection, that the cases will be described in some detail.

Sergt. M. had two typical attacks, the first from July 14 to July 26, and again from October 5 to October 12. Between the bouts of fever he was never really well, being easily tired and complaining from time to time of slight attacks of headache and pain in the legs. After the second pyrexial period symptoms continued to recur at intervals, and in February, 1916, eight months after the first infection, he still complained of them occasionally. During this month his temperature was taken regularly, night and morning, for eighteen days, when it was found that his temperature touched 99° F. on four evenings, and twice reached 99·4° F. It seems almost certain that the second febrile attack in October was a recurrence of the first in July, and not a new infection from without, and this case moreover seems to afford an example of the effects of the fever persisting for eight months.

Pte. S. was in hospital from September 11 to September 20, and again from November 26 to December 6. During the interval he complained from time to

time of aching pains in the legs, and the second attack must again be put down to a revival of the original infection.

Pte. N. was in hospital between November 5 and 14, and later between December 17 and 29. Between the two attacks he felt perfectly well, and was free from all symptoms suggestive of the disease. Here, if the second attack is to be considered dependent on the primary infection, it is an example of the virus lying absolutely dormant for a period of thirty-three days.

The Means of Transmission of the Disease.

Little evidence with regard to this was available at the time of the previous papers. The experimental evidence of McNee and Renshaw, however, which went to show that the virus was one contained in the corpuscular elements of the blood, pointed strongly to the infection being introduced by a parasite. We think sufficient proof has now been obtained that the body louse is the parasite concerned. Absolute proof is lacking, as we have been unable to carry out actual transmission experiments with lice from infected cases, but the indirect evidence given below seems to build up a good case for our view.

First of all with regard to the outbreaks in casualty clearing stations. It is noteworthy that in a small ward containing ten beds, three orderlies who have been attending cases of the disease for many months have never become infected. Thus close personal contact alone appears insufficient for infection. In another casualty clearing station, where four of the ward orderlies had typical attacks, the conditions were different. The ward was a large one, and often contained over a hundred patients, mostly slight cases of illness, and some of whom were certainly lousy when admitted. The men with 'trench fever' were kept more or less together on one side of this ward. Other men of the personnel or clearing stations affected by the disease have included :

1. The attendant of the Thresh disinfector.
2. The attendant of the incinerator.
3. A stretcher-bearer.
4. The man who had charge of the removal of soiled blankets.

These four men were never in contact with patients, but always in proximity to the clothes or blankets of cases admitted, and therefore very liable to infection with lice.

Of thirteen men in a clearing station who developed the fever, seven admitted they had seen lice from time to time on their clothes. It is further of interest that the chief outbreak in this hospital occurred three weeks after the battle of Loos, at which time many hundreds of sick and wounded were passed through in a short space of time, and attention to patients as regards lousiness was necessarily less complete than in ordinary circumstances.

Almost all the men affected by the disease state freely that they have been bitten by lice, and indeed lice have been taken off many typical cases in field ambulances and dissected, in the search for a plasmodial virus. Officers

and men are affected by this disease in about the same proportion, and for the trench zone the same holds as regards the presence of lice.

The point brought out in a previous paper that only two classes of men are affected, those from the trench zone and men of the Royal Army Medical Corps, is very important, and favours our view.   Apparently this distribution, after the disease has been continually present in our troops for over a year, must be somewhat modified, as fresh infections have recently been met with further from the front.   This is of course not surprising, when the movements of troops are considered along with the frequency of the disease and the prevalence of lice.

At first it was impossible to say whether some flying insect such as the mosquito, &c., might not be the carrier of the virus, but any such view has been negatived by the persistence of the disease unchecked throughout the whole winter.   Lice are really the only common parasites found abundantly at all seasons of the year.   It is a curious and interesting fact, when the nature of the billets in barns is considered, that fleas appear to be scarce.   They are seldom found, and are never complained of by the men themselves.

From the above evidence, necessarily not complete by the absence of experimental transmissions, it seems almost certain that the body louse must be considered the means of transmitting the disease in nature.

Incubation Period.

The only direct evidence bearing on this question is the result of the experimental inoculations.   In these the period varied from six to twenty-two days.   The shortest intervals followed the *intravenous* injection of 'whole blood', the *intramuscular* method being employed where the illness developed after twenty-two days.   It seems feasible to suppose, if the louse be the means of transmission, that much more of the virus may be introduced by an injection of 5 c.c. of blood than can be transferred by the bite of a small parasite.   We believe, from a number of observations in different cases and collections of cases, that the incubation period in nature is a fairly long one, somewhere *between fourteen and twenty-four days*.   It is impossible to give in detail a list of all the observations which have led us to define this time, but an example may be given to show the type of evidence on which we have had to depend.

Sergt. B. stated that he knew himself to be lousy on May 5, but then got rid of them by bathing and changing his clothing.   Thereafter he was not in the trenches, and was free from lice until May 21, when he was admitted to hospital with an attack of 'trench fever'.   Sixteen days thus elapsed between the time when he was lousy and the onset of his illness.

Treatment.

Before the identity of the disease was established experimentally, the treatment was naturally purely symptomatic. *Quinine*, 30 grs., along with *sodium salicylate*, 90 grs. (or sometimes *aspirin*), was given daily to reduce the temperature and relieve pain. Both of these drugs were found definitely of much value for the effects named, but it was soon obvious that neither drug cut short in the least degree the course of an attack.

Attempts were then made to find some more specific remedy, and in view of the experimental evidence pointing to the infective virus being always in the blood, arsenic was tried in the form of *salvarsan* intravenously, while *Fowler's solution* was also given to some cases by the mouth. The salvarsan was given in doses of 0·3 grm., and was administered (1) at the onset of a relapse just as the temperature was rising, (2) after a febrile period was over, to prevent a further relapse. No beneficial effect was attained, the course of the disease continuing unchecked.

Antimony, in doses of 1/50 grain intramuscularly, was given daily for a week, but the relapses followed as before, while *mercury* given by inunction and sometimes combined with *iodide of potassium* proved equally useless.

In one severe case *eusol* was given intravenously (75 c.c. of a 0·5 per cent. solution) without influencing the fever in any way.

Considering the possibility that, as occurs in other diseases, antibodies to the virus might be developed in the course of spontaneous cure, and have a therapeutic value, two cases were treated with the *serum of a carefully chosen convalescent*. Twenty cubic centimetres of blood were withdrawn from this patient ten and twelve days after his last relapse. After separation of the serum, this was injected four hours later into the veins of two patients who were just beginning to relapse on these two days. In both patients the course of the relapse was in no way altered, and subsequent relapses occurred in both men.

Thus, to sum up, no treatment hitherto tried has been in the least successful, except as regards the control of symptoms.

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